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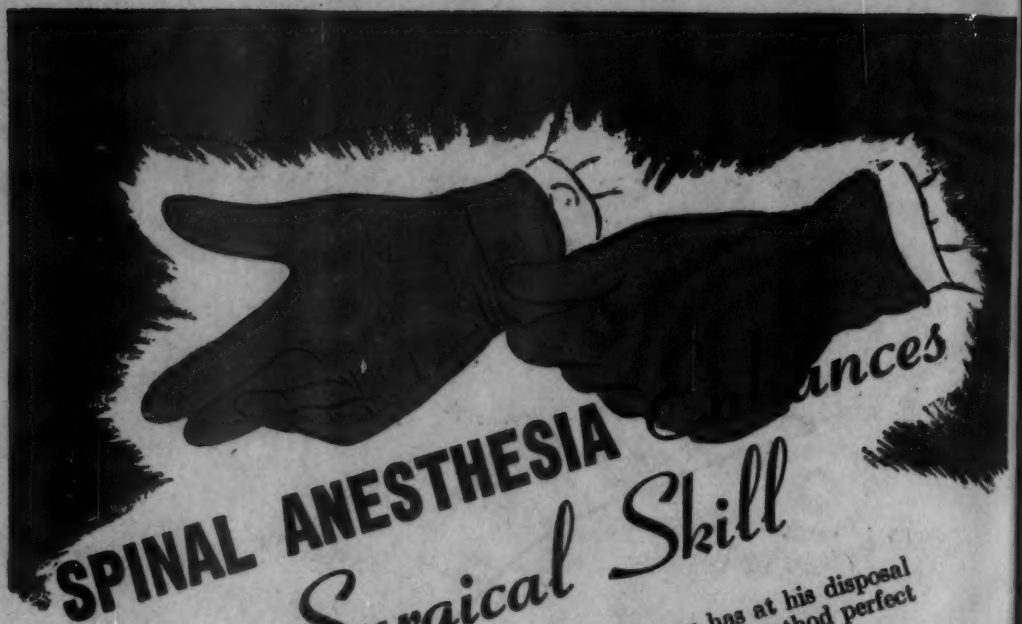

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ANNALS OF SURGERY

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CONTINUOUS SPINAL ANESTHESIA

OBSERVATIONS ON 2000 CASES

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EARLY IN 1939, we conceived the idea of continuous spinal anesthesia. A method was formulated, and used on experimental animals. It worked. A great many anesthesias were given dogs, rabbits and monkeys by the method of leaving a needle in the subarachnoid space and giving repeated small doses of procaine hydrochloride. We found that profound anesthesia could be produced and maintained for an unlimited time by this method, without causing any detectable damage to the animal or its functions. Monkeys were kept anesthetized for periods as long as 12 and one-half hours, without any toxic symptoms. It was also observed that large single doses would cause toxic symptoms, and death, but that the same total dosage given over a relatively long period of time caused no toxic symptoms. On April 10, 1939, we administered the first continuous spinal anesthesia to a human being. Since then, we have given well over 2,000 anesthesias by this method, and in this communication we are reporting some of our observations and impressions on these cases.

The method consists merely of making and maintaining a spinal puncture, with an initial injection of an anesthetic agent into the subarachnoid space, and the subsequent additional injections of the agent as it is needed, much the same as ether is administered, in dosage sufficient to obtain the desired result.

In this series of cases we have used procaine hydrochloride as the anesthetic agent, with one exception, when we used metycaine, because the patient was sensitive to procaine. Procaine was chosen deliberately, because we believe that it is the least toxic of all the drugs used for this purpose, and it has the most fleeting action of all the drugs of this nature. By its use, we have been able to have all the advantages of spinal anesthesia, but have been able to use it with a great degree of control and safety.

The disadvantages of the single-dose method of spinal anesthesia are: (1) failure of the single dose to produce the level and degree of anesthesia desired; (2) failure of the anesthesia to last for the length of time required to perform the procedure; and (3) the impossibility of removing any of the

agent once it has been injected, should toxic symptoms appear. Continuous spinal anesthesia overcomes the first two disadvantages with ease, and it was accidentally discovered that after the injection had been made, spinal fluid containing the drug could be aspirated and the nerves would promptly recover from the effect of the drug. This has been repeated a number of times, and has been definitely established.

We believe the toxic effects of a spinal anesthetic agent are due to the absorption of the drug into the venous circulation. This can be minimized by the injection of relatively small doses of the drug. Anesthesia is maintained by the concentration of the drug in the spinal fluid which bathes the spinal cord and nerve roots. This concentration may be maintained by relatively small additional doses, given at certain time intervals. In this way, very large doses may be administered with little toxic reaction.

TECHNIC OF ADMINISTRATION

The technic of administering continuous spinal anesthesia is very simple. A few pieces of specialized equipment are necessary, which are, (1) a special mattress, five inches thick, with an opening to permit the needle to project from the back of the patient; (2) a special malleable needle; and (3) a 30-inch piece of small bore, thick-walled rubber tubing, with special Luer-Lok connections and stopcock. The other items of equipment used are entirely standard and are usually available in any hospital. Plate I illustrates the fully prepared tray as we use it for continuous spinal anesthesia.

For the puncture, the patient is placed in the lateral decubitus, with the back toward the side of the mattress with the opening. A sterile towel is placed over the upper flank and hip, and the back is prepared with a skin antiseptic. The site of the puncture is selected, chiefly by the individual characteristics of the immediate patient, but usually the third or fourth lumbar interspace is chosen. The space that appears to be the easiest through which to make the puncture is the deciding factor. The skin is anesthetized by the introduction of 1 cc. of 1 per cent procaine hydrochloride with 50 mg. of ephedrine sulphate. The latter drug is used to combat the physiologic lowering of blood pressure which nearly always accompanies the production of spinal anesthesia. The skin is then punctured with a Sise needle introducer. It is important that only the skin be punctured and not the interspinous ligament, for it is the firm grip of the ligament on the needle that maintains the needle in position during the anesthesia. The puncture is now made, and the success or failure of this step determines the success or failure of the method. The needle is a special one, made of a very malleable metal, and therefore, bends with ease. The needle is grasped between the thumb and forefinger, about one-half inch from the point and is started on its way. The position of the needle should be such that it is perpendicular to the back. The only deviation from this simple rule is that the needle may be inclined slightly upwards. The puncture should be made in the exact midline of the body,

and midway between the two lumbar spines. Once the needle has entered the interspinous ligament, it is impossible to change its course, thus, the importance of starting right. The needle is then advanced, always keeping a very short grasp from the skin in order to keep the needle from bending. When the dura is penetrated, the characteristic snap is felt and the puncture is either made or may be completed by advancing the needle a very short distance further. Rotating the needle will often assist in obtaining a free flow of spinal fluid. If a successful puncture is not made, the needle should be withdrawn and a new puncture made. Since we do not use stylets, it is important that the patency of the needle be proven before every attempt by flushing it with sterile water or by forcing air through the needle by use of a syringe.

After the puncture has been made, a 10 cc. Luer-Lok syringe is attached to the needle and 10 cc. of spinal fluid is aspirated. This must be accomplished without too much pulling on the plunger of the syringe. Often the fluid will flow into the syringe, but cannot be aspirated. Gentle traction on the plunger of the syringe is the rule. The syringe is removed, and the needle plug is placed in the needle to prevent the excessive loss of spinal fluid. The 10 cc. of spinal fluid is now used to dissolve 500 mg. of procaine hydrochloride, which is done in the ampoule by the use of an ordinary intravenous needle and the syringe. After the crystals have dissolved, the solution is drawn up into the syringe and the rubber tubing is attached to the syringe; 2 cc. are forced into the tubing, which displaces the air, and fills the tubing with the procaine solution in spinal fluid. Now, the tubing is attached to the spinal needle and the initial injection is made. This dose varies, as will be discussed later, but usually is 3 cc., or 150 mg. of procaine. After the injection is made, the fluid is aspirated to determine if a satisfactory return flow is present. The stopcock is then closed and the patient is turned on his back, or placed in position for operation. This must be done with care, to prevent the needle from being displaced. The needle should not touch the mattress at any point, nor should it touch the top of the operating table.

The most important factor in the success of continuous spinal anesthesia is the making and maintaining of a good puncture, which is evidenced by the ability to aspirate spinal fluid at any time. If a free return flow is not obtained, the needle may be adjusted through the opening in the mattress, and no operation should be started until the puncture is satisfactory.

Usually, the effect of the drug is obtained in about 90 seconds after the injection. If after the lapse of two or three minutes, the anesthesia is not satisfactory, the stopcock is opened and another dose is given, which is usually 1 cc., or 50 mg., of procaine. Once satisfactory anesthesia has been produced, it may be maintained by the subsequent injections of 50 mg. every 30 minutes. This is not a hard and fast rule, but it will suffice for most cases. The dose is enough, and if more is needed, it must be given. We have encountered cases which required additional doses every 15 minutes, and needed large doses, but many cases do not need it so often nor so much.

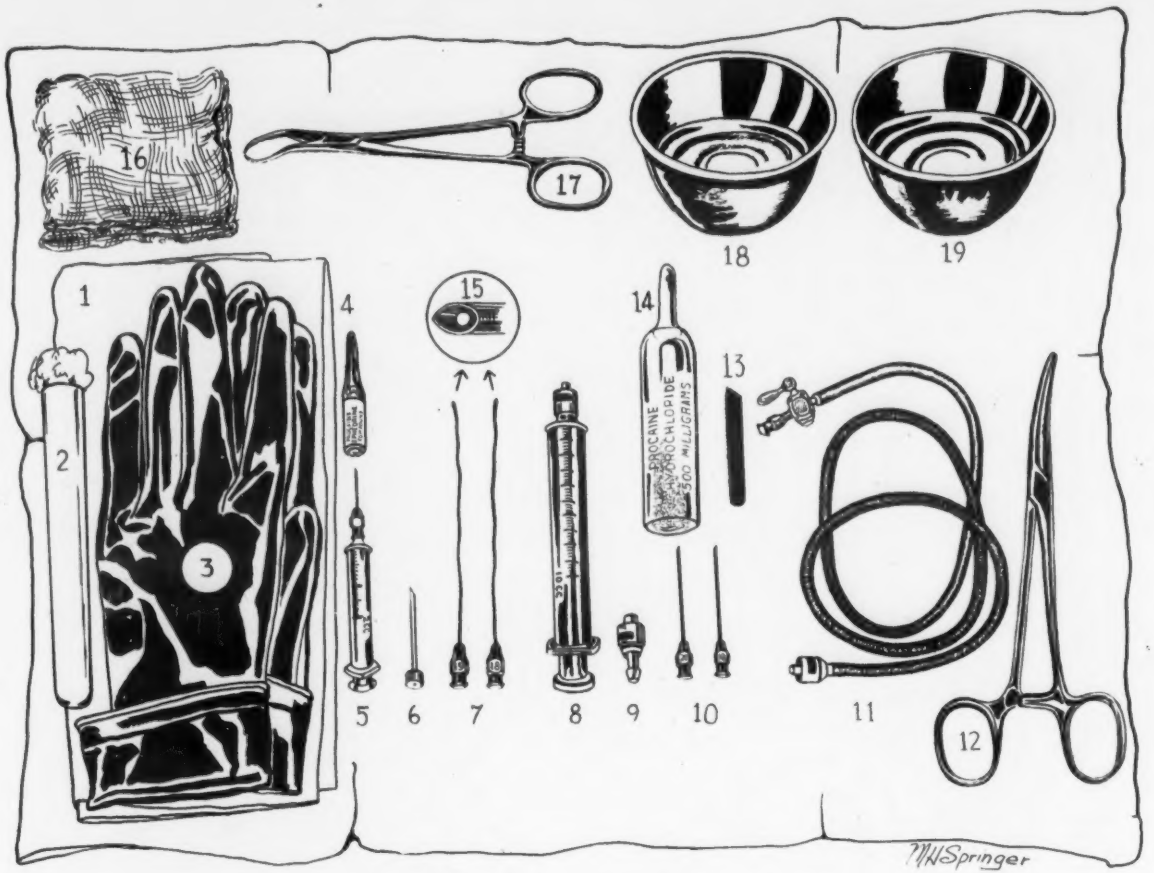

PLATE 1. Complete tray for continuous spinal anesthesia.

1. Two towels. 2. Talc. 3. Rubber gloves. 4. Ampoule containing 1 cc. 1 per cent procaine hydrochloride and 5 per cent ephedrine sulphate. 5. Hypodermic syringe and needle. 6. Sise needle introducer. 7. Lemmon continuous spinal needles, 18- and 19-gauge. 8. 10 cc. Luer-Lok syringe. 9. Luer-Lok needle plug. 10. Two intravenous needles. 11. Special rubber tubing with Luer-Lok connections and stopcock. 12. Hemostat. 13. Glass file. 14. Ampoule containing 500 mg. procaine hydrochloride. 15. Point of Lemmon needle, showing short bevel and counter opening. 16. Gauze sponges. 17. Towel clip. 18. Cup for sterile water. 19. Cup for skin antiseptic.

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introducer. 7. Lemmon continuous spinal needles, 16- and 17-gauge. 8. Luer-Lok needle plug. 9. Luer-Lok needle plug. 10. Two intravenous needles. 11. Special rubber tubing with Luer-Lok connections and stopcock. 12. Hemostat. 13. Glass file. 14. Ampoule containing 500 mg. procaine hydrochloride. 15. Point of Lemmon needle, showing short bevel and counter opening. 16. Gauze sponges. 17. Towel clip. 18. Cup for sterile water. 19. Cup for skin antiseptic.

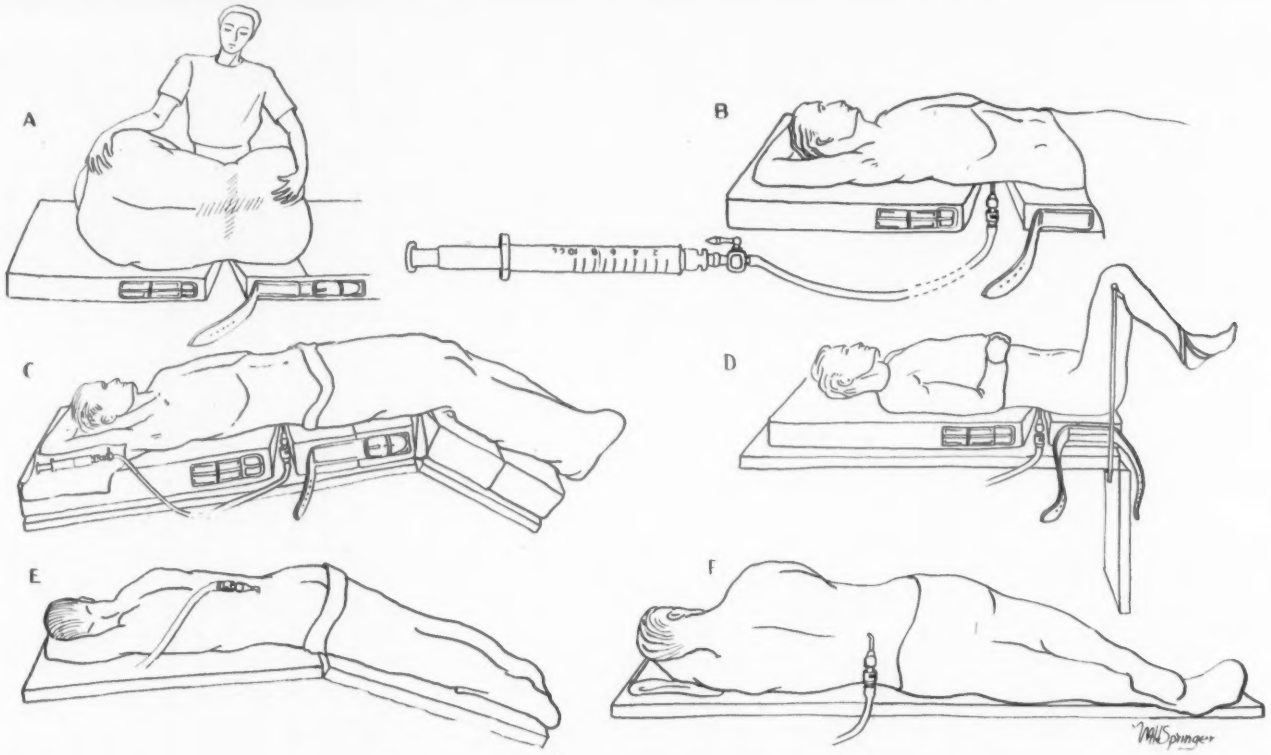

PLATE 2. Special mattress for continuous spinal anesthesia.

FIG. A. Position of patient on special mattress for spinal puncture.

FIG. B. Patient lying on back, with opening in mattress for adjusting needle.

FIG. C. Patient in position for operation, showing syringe in sterile towel. Syringe and towel are fastened to mattress by towel clip. Strap on side of mattress is buckled during operation.

FIG. D. Patient in perineal position. Lower half of mattress is detached.

FIG. E. Patient in prone position for operations on back, anal region or posterior surface of extremities.

FIG. F. Patient in Sims' position. Needle is bent at skin and fastened with adhesive. No special mattress is needed for the last two positions.

PRELIMINARY MEDICATION

We feel that one of the most important steps in the production of a satisfactory spinal anesthesia is the administration of the proper preliminary medication. Many patients are apprehensive, and fear being awake for the operation. Also, the operation of spinal puncture is not without pain in the unsedated patient. Our routine is to give the patient 3 gr. of nembutal the night before operation, followed by another similar dose three hours before operation. One hour before operation, a hypodermic injection of morphine sulphate gr. ¼ and scopolamine hydrobromide gr. $\frac{1}{100}$ is given. This dosage is for the average good-risk adult who is not seriously ill. The dosage is altered to suit the individual case; in the aged and very ill, the dosage is cut sharply. If a patient appears in the operating room with evidence of insufficient sedation, additional doses of morphine are given until the desired effect is obtained. We often give this intravenously. If during the operation, we feel that the patient needs more sedation, it is repeated, usually in ⅛ gr. doses. It is a well known fact that certain unpleasant sensations are not abolished by spinal anesthesia, which are satisfactorily cared for by the use of sedatives. The complaint of the patient of pain in the chest from traction on the cecum during appendicectomy is an illustration of pain which is carried by way of the sympathetics, which often involve thoracic segments, and could be controlled only by very high spinal anesthesia, but is easily abolished by the judicious use of sedatives.

We have found that children tolerate morphine very well. We have given relatively large doses to children, in divided doses, of course, with no ill effects. We have not encountered respiratory depression from its use. In fact, in this series of cases, we had no complications of a respiratory nature in any of our patients under the age of 15 years, of which we had 66.

TREATMENT DURING THE OPERATION

Other than the preliminary dose of ephedrine given with the procaine for skin anesthesia, we seldom use any vaso-pressor drugs during the course of the anesthesia and operation. It is our firm belief that if a patient is able to stand the surgery, the use of continuous spinal anesthesia will not contribute any deleterious effects. Of course, we have patients whose blood pressure falls quite low during the course of a difficult and shocking operation, but it is treated with the thought of treating the operative shock rather than as treating low blood pressure due to spinal anesthesia. For this reason, we gave our patients intravenous glucose solution, blood, or plasma to combat this condition and rarely use the vaso-pressor drugs. We anticipate such complications, and never is an operation undertaken on a serious risk, nor is a shocking operation begun until there is flowing into the patient's veins ample fluids, with whole blood, plasma, or both immediately available. In this manner we have been able to keep our patients in good condition during the operation. We believe in, and practice, the administration of oxygen throughout the anesthesia and operation.

ANALYSIS OF CASES

We are presenting 2000 cases in which we have employed continuous spinal anesthesia. Our records show that in three cases we did not get satisfactory anesthesia. One case developed uncontrollable cough during the course of a pulmonary lobectomy. The patient was given cyclopropane during the stage of tugging on the bronchus which caused the coughing. Sensory anesthesia at this time was at the level of the hyoid bone. In the two other cases, faulty technic and a busy schedule are to blame. They were both simple pelvic operations and neither patient was anesthetized to the degree that operation could be undertaken. They were both given ether anesthesia. Let us explain that many of the anesthesias in this series were given by internes and relatively inexperienced anesthetists. Many of the cases in this series have been saved from being failures by the authors making new punctures after what had been thought to be a satisfactory puncture had failed to produce satisfactory anesthesia. In several cases, the patient has been repunctured after the abdomen had been opened and perfectly satisfactory anesthesia obtained.

Age.—The average age for this group was 35.9 years. The youngest was two days old, who was operated upon for congenital occlusion of the jejunum. A cholecystectomy and choledochostomy for stones on a man, age 87, represents the eldest of the series. With our increased experience with this type of anesthesia in children, we have found that it is very satisfactory. In the last 1000 cases, we have had 33 who were ten years or less, and 33 between ten years and fifteen. There were eight cases of five years or less. This has been made possible by the liberal use of morphine in multiple small doses, which we have found is very well tolerated by children. We have not encountered the profound respiratory depression in its use, and we do not fear to use the drug in very young children.

Length of Operations.—The average length of the operations in this series was 50.1 minutes. The longest procedure was a subtotal pancreatectomy which required five hours and 25 minutes. The shortest procedure was about two minutes for the incision and drainage of an abscess.

Dosage.—The dosage of procaine for continuous spinal anesthesia is a variable factor. For the operations in this series, the total dosage per case averaged 210.9 mg. The average number of injections was 2.37. The smallest dose was 20 mg. for the amputation of a toe. The largest dose given to one patient was 2200 mg. This was for a hysterectomy which required 35 minutes operating time.

In general, for the average case we give an initial dose of 150 mg., which will usually give satisfactory anesthesia for any type of abdominal surgery. This is usually followed by an additional injection of 50 mg. every half hour for the remainder of the operation. However, we encounter many cases which do not require as much, and also many cases which require much larger doses. Children tolerate the drug very well, and will require rela-

tively much larger doses than adults. We have on many occasions had to give as much as 250 mg. to a child of seven years in order to obtain satisfactory anesthesia to perform an appendicectomy, which of course, required no additional doses after anesthesia was produced. We have performed a suprapubic prostatectomy on a man of 85 years, which required 60 minutes, with a total dose of 50 mg. The aged and very ill require very small doses. The dosage for any one case may be simply stated as being enough to complete the operative procedure. The condition of the patient is checked frequently, and sufficient dosage is given to produce the desired result. The longest procedure in our series was a subtotal pancreatectomy which required five hours and 25 minutes. This patient received 1450 mg. of procaine, given in 18 injections.

Our routine procedure calls for the use of a 5 per cent solution of procaine in spinal fluid. Additional doses may be prepared in sterile distilled water or normal saline solution. We have used various dilutions from 1 to 10 per cent, but have found that the 5 per cent solution is the most satisfactory.

EFFECT ON BLOOD PRESSURE

The blood pressure, pulse and respiration are checked and recorded every five minutes during the anesthesia. Following the injection of ephedrine along with the procaine which is used to anesthetize the skin for the puncture and to support the blood pressure, we regularly noted an increase in the pressure, which was soon followed by a lowering of the pressure to the original level, or slightly below. Unless the operation was of a shocking nature we did not encounter any great fall in the systolic pressure. The average systolic pressure at the beginning of operation for this series was 127 millimeters of mercury. The average systolic pressure at the conclusion of the operation was 114.3 millimeters of mercury. The average fall of systolic pressure was only 12.7 millimeters of mercury. We have had a number of cases in which the blood pressure reached, and maintained, a higher level than that before the anesthesia was begun. This, however, is an exception to the rule. During the course of operations, we have had pressures as low as 40 Mm. Such cases were treated by infusions of glucose solution, blood or plasma. Seldom do we use the vasopressor drugs. To cite an example, during the course of a radical mastectomy the blood pressure dropped to 40 Mm. of mercury. The patient's exposed chest wall was covered with hot sponges, no further dissection was done, an intravenous of plasma was started, and in about ten minutes the blood pressure was at 100 Mm. of mercury. The operation was then resumed and completed with the patient in good condition. We feel that instances such as this prove that it is the surgery and not the anesthesia which causes the excessive falls in blood pressure.

Headache.—The incidence of headache following the use of continuous spinal anesthesia is about the same as following the use of the single-dose

spinal. It is a very difficult thing to understand or explain. It appears to be more frequent following simple procedures than the more serious ones. Our incidence of headache for the entire series is 3.1 per cent. This problem is a relatively minor one, which usually responds to simple treatment, such as the administration of aspirin, and we feel that it is a very low price to pay for the advantages of spinal anesthesia, both to the patient and the surgeon.

Urinary Retention.—We have made it a rule to use an indwelling catheter in patients who are submitted to operations which may last a relatively long time, and who are receiving intravenous during the operation. The bladder often distends during the operation, and if not taken care of tends to encourage retention. We also use an indwelling catheter in all vaginal plastic cases. Our incidence of retention, excluding the above mentioned cases, is 3.3 per cent for the series.

Pulmonary Complications.—In this series, there were 45 cases which developed pulmonary complications, 27 of these were bronchopneumonia, 11 were lobar pneumonia, five were atelectasis, and two were pulmonary embolism.

Nerve System Complications.—One case developed anesthesia of the upper lip immediately following a cystoscopic examination. This persisted for two days, then disappeared completely. There was nothing unusual about the anesthesia, the level was not high, and we cannot explain this occurrence on any other basis except hysteria. There were no other incidences of any type of neurologic complications.

Mortality.—There were 82 deaths in this series of 2000 cases making a gross mortality of 4.1 per cent. The average time that elapsed between operation and death was 5.9 days. None of these were anesthetic deaths, and we do not feel that the anesthesia was a contributing factor in any of them. Thirty-six of those that died were suffering with malignant growths. There were 18 deaths from diffuse peritonitis. The other deaths were due to many conditions, including pulmonary, cardiac, renal and hepatic conditions. One death was due to hemorrhage from a far-advanced carcinoma of the cervix, the anesthesia being given for the operation of packing of the vagina and rectum. We have not had a single death due directly to the use of continuous spinal anesthesia.

Table I is an outline of the operations performed on the cases in this series.

SUMMARY

1. We have discussed the experimental work which paved the way to the use of continuous spinal anesthesia.

2. We have given a detailed account of the technic of continuous spinal anesthesia.

3. Two thousand operations are reported which have been done under continuous spinal anesthesia, and some of the important observations made on this series are presented

TABLE I

OUTLINE OF 2000 CASES DONE UNDER CONTINUOUS SPINAL ANESTHESIA

Gastro-intestinal Operations:	
Stomach	68
Appendix	497
Intestinal and colon	97
Biliary tract operations	187
Hernia operations	223
Nerve system operations	34
Gynecologic Operations:	
Perineal	93
Abdominoperineal	206
Abdominal	123
Obstetric operations	140
Urologic operations	89
Proctologic operations	87
Cardiovascular operations	21
Thoracic operations	48
Orthopedic operations	69
Miscellaneous operations	18

CLASSIFICATION

Gastro-intestinal Operations:		68
Stomach Operations:		
Total gastrectomy	4	
Total gastrectomy with splenectomy	1	
Subtotal gastrectomy	9	
Subtotal gastrectomy and appendicectomy	19	
Subtotal gastrectomy and resection of third part duodenum and trans. colon	1	
Anterior gastro-enterostomy	7	
Posterior gastro-enterostomy	2	
Closure duodenal ulcer, cholecystectomy and appendicectomy	2	
Closure spontaneous rupture of stomach	1	
Resection of bleeding gastric ulcer	1	
Cholecystogastrostomy	2	
Cholecystojejunostomy	1	
Biopsy carcinoma of stomach	1	
Biopsy head of pancreas	1	
Subtotal gastrectomy and cholecystectomy	5	
Closure perforated ulcer	7	
Closure perforated gastric carcinoma	1	
Gastrostomy	1	
Subtotal pancreatectomy	1	
Resection tail of pancreas and splenectomy	1	
Appendix Operations:		497
Appendicectomy	395	
Appendiceal abscess drainage	15	
Appendicectomy and excision of ovarian cyst	33	
Appendiectomy and salpingo-oophorectomy	11	
Appendicectomy and uterine suspension	18	
Appendicectomy and lysis adhesions	20	
Appendicectomy and reduction of torsion of omentum	1	
Appendicectomy and excision of varicocele	1	
Appendicectomy and myomectomy	1	
Appendicectomy and cecostomy	1	
Appendicectomy ahd fecal fistulectomy, and incisional herniorrhaphy	1	
Intestinal and Colon Operations:		97
Abdominal and perineal resection of rectum	12	
Closure of colostomy	6	
Mikulicz resection splenic flexure	3	
Mikulicz resection of sigmoid	8	
Resection ileum—intestinal obstruction	5	
Lysis of adhesions and reperitonealization for intestinal obstruction	27	
Incision and drainage subhepatic abscess	1	
Abdominal section—biopsy of liver	10	
Resection sigmoid primary anastomosis	1	
First stage Lahey	3	

TABLE I (Continued)

Second stage Lahey	1	
Colostomy	6	
Cecostomy	2	
Closure of cecostomy	1	
Resection ileum for intussusception	1	
Ileotransverse colostomy	5	
Ileosigmoidostomy	1	
Closure of fecal fistula	1	
Excision of duodenal diverticulum and appendicectomy	1	
Excision of Meckel's diverticulum	1	
Exteriorization of sigmoid for diverticulitis	1	
Biliary Tract Operations:		187
Cholecystectomy	49	
Cholecystectomy and lysis of adhesions	25	
Cholecystectomy and appendicectomy	57	
Cholecystectomy and T-tube drainage of common bile duct	35	
Cholecystectomy and hysterectomy	2	
Cholecystectomy and oophorectomy	2	
Cholecystectomy and choledochojejunostomy and jejunojejunostomy	2	
Cholecystostomy	2	
Choledochostomy	6	
Cholecystogastrostomy and biopsy of head of pancreas	2	
Cholecystojejunostomy	1	
Cholecystectomy and anterior gastro-enterostomy	1	
Excision of stricture of common bile duct	1	
Excision of tumor of common bile duct	1	
Repair of divided common bile duct	1	
Hernia Operations:		223
Unilateral inguinal herniorrhaphy	103	
Right inguinal herniorrhaphy and appendicectomy	49	
Strangulated inguinal hernia	6	
Bilateral inguinal hernia	23	
Femoral herniorrhaphy	9	
Ventral herniorrhaphy	5	
Incisional herniorrhaphy	11	
Inguinal herniorrhaphy and excision of hydrocele	1	
Umbilical herniorrhaphy	4	
Umbilical herniorrhaphy and appendicectomy	3	
Incisional herniorrhaphy, cholecystectomy, and appendicectomy	1	
Incisional herniorrhaphy and hysterectomy	1	
Incisional herniorrhaphy and myomectomy	1	
Femoral herniorrhaphy and closure of ileostomy	1	
Inguinal herniorrhaphy and D and C, cauterization of cervix and appendicectomy	1	
Inguinal herniorrhaphy and orchidectomy	1	
Herniotomy and appendicectomy	1	
Herniotomy and exteriorization of gangrenous ileum	1	
Richter's hernia	1	
Nerve System Operations:		34
Presacral neurectomy	1	
Presacral neurectomy and appendicectomy	1	
Presacral neurectomy, uterine suspension and appendicectomy	17	
Presacral neurectomy, and D and C	2	
Presacral neurectomy and hysterectomy	3	
Bilateral lumbar ganglionectomy	3	
Cervical ganglionectomy	2	
Thoracic ganglionectomy	1	
Unilateral thoracic and lumbar ganglionectomy	3	
Exploration and freeing of adhesions of common peroneal nerve	1	
Gynecologic Operations:		93
Perineal:		
Dilatation and curettage	29	
Dilatation and curettage, radium	20	
Induction of therapeutic abortion	1	
Dilatation and curettage and biopsy	2	
Dilatation and evacuation	2	
Vaginal hysterectomy and perineorrhaphy	10	
Fothergill, anterior and posterior colporrhaphy and perineorrhaphy	4	

TABLE I (Continued)

Plastic repair	22	
Excision of anterior vaginal wall	1	
Vesicovaginal fistula	1	
Vaginal packing for hemorrhage (carcinoma of cervix)	1	
Abdominal and Perineal:		206
Plastic and section	105	
Plastic and appendicectomy	14	
Plastic and hysterectomy	7	
Dilatation and curettage, cauterization of cervix, hysterectomy, salpingo-oophorectomy and appendicectomy	76	
Plastic and section, hysterectomy and cholecystectomy	3	
Amputation of cervix and cholecystectomy	1	
Abdominal:		123
Supravaginal hysterectomy	22	
Unilateral salpingo-oophorectomy	14	
Bilateral salpingo-oophorectomy and appendicectomy	5	
Unilateral salpingo-oophorectomy and appendicectomy	4	
Hysterectomy, bilateral salpingo-oophorectomy and appendicectomy	49	
Excision ovarian cyst and appendicectomy	10	
Hysterectomy and appendicectomy	6	
Uterine suspension and appendicectomy	4	
Anastomosis of uterine tube	1	
Biopsy carcinoma of uterus	1	
Bilateral oophorectomy and resection of ileum	1	
Drainage of pelvic abscess	1	
Supravaginal hysterectomy and presacral neurectomy	2	
Resection of ovarian cysts and lysis of adhesions	2	
Myomectomy and appendicectomy	1	
Obstetric Operations:		140
Cesarian section	73	
Cesarian section and ligation of tubes	55	
Cesarian section and appendicectomy	3	
Cesarian section and incisional hernia	2	
Cesarian section and lysis of adhesions	5	
Cesarian section and repair of ruptured uterus	1	
Vaginal cesarian section	1	
Urologic Operations:		89
Suprapubic prostatectomy	17	
Perinephritic abscess	1	
Ureterolithectomy	5	
Nephrectomy	7	
Excision of varicocele	6	
Nephrolithectomy	1	
Hydrocele and circumcision	1	
Hydrocele	3	
Orchidectomy	5	
Lysis of adhesions obstructing ureter	1	
Aberrant renal vessels causing obstruction	1	
Bilateral vasotomy	1	
Cystotomy	2	
Excision cyst urachus, appendicectomy	1	
Excision epididymis	1	
Nephropexy	2	
Meatomy and plastic of glans penis	1	
Excision of diverticulum bladder	1	
Excision of carcinoma of bladder	1	
Cystectomy	1	
Vesico-abdominal fistulectomy	1	
Cystoscopy	22	
Dilatation of ureteral stricture	1	
First stage Torek	4	
Second stage Torek	2	
Proctologic Operations:		87
Hemorrhoidectomy	62	
Excision of fistula in ano	13	
Incision and drainage ischiorectal abscess	5	
Biopsy and fulguration anorectal tuberculosis	1	

TABLE I (Continued)

Fulguration anorectal tuberculosis	2	
Sigmoidoscopic examination	2	
Sigmoidoscopic and biopsy	1	
Repair of complete laceration rectal sphincter	1	
Orthopedic Operations:		69
Sequestrectomy, osteomyelitis	3	
Excision head of metatarsal	1	
Bilateral amputation hammer toe	2	
Excision internal semilunar cartilage	5	
Reduction fracture of 5th metatarsal	1	
Excision pilonidal sinus	32	
Excision benign tumor of leg	7	
Excision coccyx	6	
Mid thigh amputation	6	
Open reduction fracture great toe	1	
Excision bunions	1	
Excision exostosis	1	
Excision of lipoma thigh	1	
Excision popliteal bursa	1	
Removal of transverse process 5th lumbar vertebra	1	
Cardiovascular Operations:		21
Ligation of patent ductus arteriosis	1	
External ileofemoral arteriovenous aneurysm	1	
Right femoral embolectomy	1	
Bilateral saphenous ligation	11	
Unilateral saphenous ligations	7	
Thoracic Operations:		48
Revision of wound	1	
Anterior thoracoplasty, 1st stage	6	
Posterior thoracoplasty, 1st stage	5	
Posterior thoracoplasty, 2nd stage	6	
Posterior thoracoplasty, 3rd stage	3	
Posterior thoracoplasty, 4th stage	1	
Pulmonary lobectomy	2	
Pneumonectomy	2	
Radical mastectomy	9	
Simple mastectomy	1	
Excision of breast tumor	10	
Breast plastic	2	
Miscellaneous Operations:		18
Incision and drainage abdominal abscess	5	
Repair of evisceration	3	
Incision and drainage of abscess	2	
Lipectomy and ventral herniorrhaphy	1	
Excision of carbuncle	1	
Excision of sarcoma of popliteal space	1	
Resection of inguinal lymph nodes	1	
Resection of strangulated omentum	1	
Removal of bullets from leg	1	
Incision and drainage stab wound thigh	1	
Excision of ulcer of abdominal wall	1	

4. The use of continuous spinal anesthesia in children has been indicated.

5. We wish to emphasize the adequacy, safety and controllability of this method.

6. The fact that the dosage is a most variable factor is emphasized, and we reiterate that the dose is enough to produce the desired level and degree of anesthesia.

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CONTINUOUS SPINAL ANESTHESIA FOR LABOR AND DELIVERY*

A PRELIMINARY REPORT

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IN 1942 HINGSON AND EDWARDS[1] through a familiarity with the continuous spinal anesthesia method introduced by Lemmon,[2] first published their report on continuous caudal analgesia in obstetrics. The effect of this work was to stimulate anew, widespread interest in painless childbirth. Both the advantages and the inherent dangers of the method have been subjected to critical analysis by many investigators. It is generally agreed that the most important cause of failure is the inability to insert the needle properly into the caudal canal. We decided, therefore, to investigate the possibility of continuous spinal anesthesia. While the method has been used for some time in cesarean section, this is the first attempt, to our knowledge, to apply it to labor and vaginal delivery. This preliminary report is based on our experience in its use on fifty cases.

METHOD

The technic employed has not been entirely uniform. In the first five cases we followed the principle as originally advocated by Lemmon[2] using a standard continuous spinal set with a 19 gauge malleable nickel needle. In our desire to keep the anesthesia as low as possible the third or fourth lumbar interspace was chosen as the site of injection. The anesthetic agent was procaine hydrochloride 5 per cent in normal saline. The standard dose was 15 mg. With this technic relief of pain usually occurred within five minutes. However, in most instances the patient experienced dull pain in the back with each uterine contraction. This unfavorable reaction prompted us to inject at a higher level. When this was done the relief of pain was complete within three minutes. While the choice of the first or second interspace may seem to many unnecessarily high, this location is physiologically correct. The truth of this statement can be verified by examination of the chart in Figure 1 showing the sensory pathways to the uterus. The average interval between injections using a 5 per cent procaine hydro-

* We are indebted to Dr. Robert A. Hingson for his cooperation in the preparation of this report.

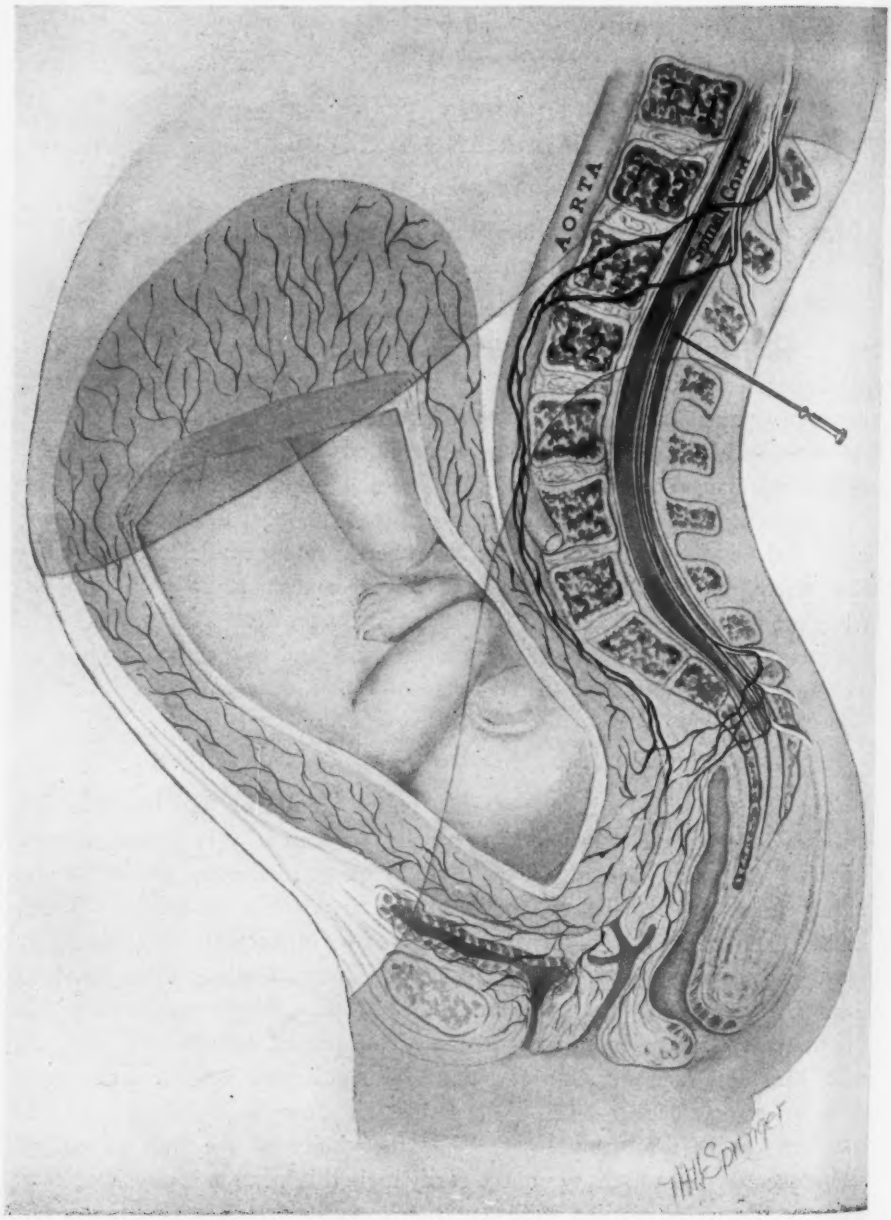


FIG. 1.—Sagittal section of a pregnant woman showing spinal needle in place between the first and second lumbar vertebrae. Note the needle's proximity to (1) the eleventh and twelfth thoracic nerves which carry uterine sensory fibers, and (2) the second, third, and fourth sacral nerves which carry sensory fibers from the cervix and lower birth canal.

Puncture of the dura at a higher level might result in injury to the spinal cord. Motor fibers, not shown, are involved if the anesthesia blocks the sixth or higher thoracic nerves.

chloride was 30 to 40 minutes. Two per cent procaine hydrochloride was then tried. This was found to be unsatisfactory for two reasons; namely, a higher dosage requirement (20 mg.) and a shorter interval between doses (15 to 20 minutes). Despite the fact that our results in these early cases were encouraging, we were not satisfied with this method primarily because of the length of the needle and the difficulty in keeping it in the subarachnoid space with the inevitable motion of the patient while in labor.

Our present technic is as follows: the patient is placed on either side with the back flexed, which is the most favorable position for lumbar puncture. After a thorough surgical preparation a 2.5- or 3-inch malleable steel needle of the type used by Hingson and Edwards in caudal anesthesia is inserted into the first or second lumbar interspace. A free drip of spinal fluid is obtained. The back is then extended in order to fix the needle firmly. The needle is then connected by rubber tubing to a 20 cc. Luer-Lok syringe with cut off valve containing 1.5 per cent Metycaine in Ringer's solution. The standard dose is 15 mg. (1 cc.) which is repeated at necessary intervals to secure complete relief of pain (25 to 40 minutes). The height of the anesthesia level is tested at frequent intervals. We have found the sensory loss should extend 2 to 3 cm. above the umbilicus. Should the level rise above this point, there is danger of causing a cessation of uterine contractions. It is important that while we have found this dosage sufficient to produce anesthesia, complete motor paralysis does not occur. In practically all cases the needle was withdrawn when the patient was placed on the delivery table, due to the fact that a split-mattress was not available. In our opinion this is undesirable because it destroys an important safety factor, namely the ability to withdraw the anesthetic agent in the event of any untoward effect of the anesthetic solution.

In several patients spinal fluid was withdrawn following the delivery in order to determine the Metycaine content. Report of one specimen from the laboratory of Eli Lilly and Company is as follows:

> "J. S., age 31, para 1—continuous spinal July 6/44, 8 cc. Spinal fluid withdrawn following delivery. The specimen as measured in our laboratory contained 7.5 cc. The concentration was 4.9 mg. "metycaine" (*gamma* [2-methylpiperidino]-propyl benzoate hydrochloride, Lilly) per cc. or a total quantity of about 37 mg. This patient received 60 mg. of metycaine over a period of two hours."

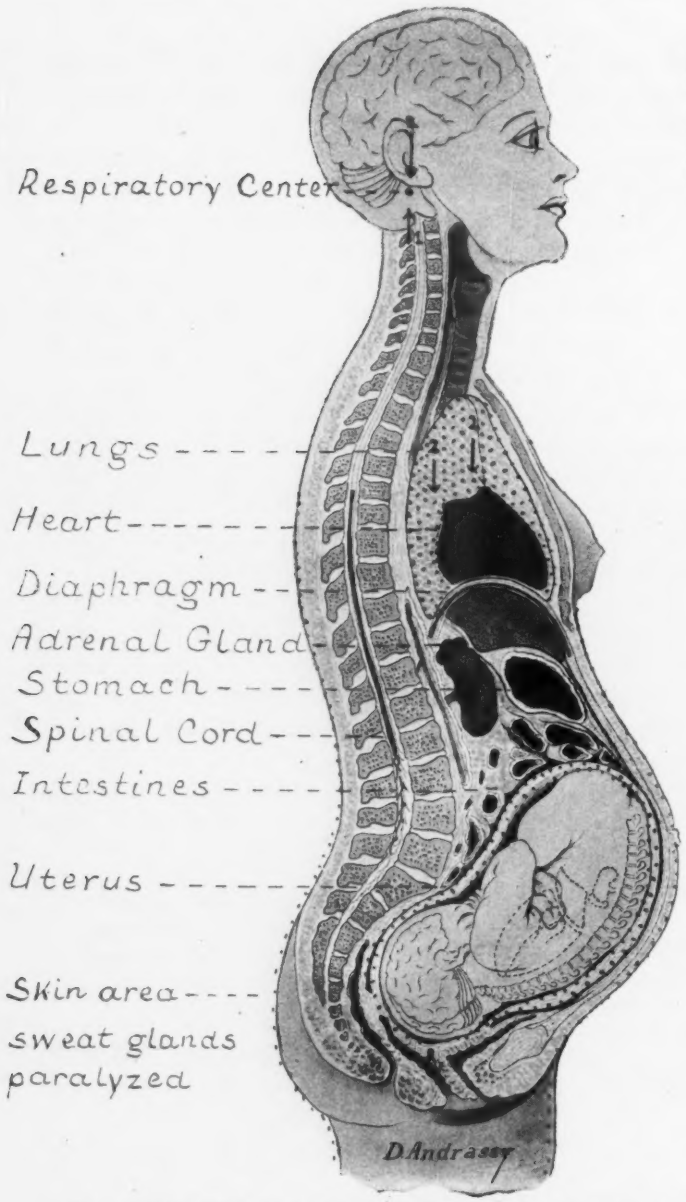
The presence of this concentration of the anesthetic in the spinal fluid serves to emphasize the desirability of keeping the needle in place until completion of the delivery.

RESULTS

Complete relief of pain was obtained in 40 cases, or 80 per cent, partial relief of pain was obtained in eight cases or 16 per cent. Two cases, or 4 per cent, were complete failures despite the fact that in each instance a free flow of spinal fluid was obtained and an adequate dose of anesthetic administered. In three cases, or 6 per cent, the anesthetic was discontinued because of

SPINAL AND CONTINUOUS SPINAL ANESTHESIA

Metycaine, Procaine, Pontocaine, Nupercaine, Monocaine



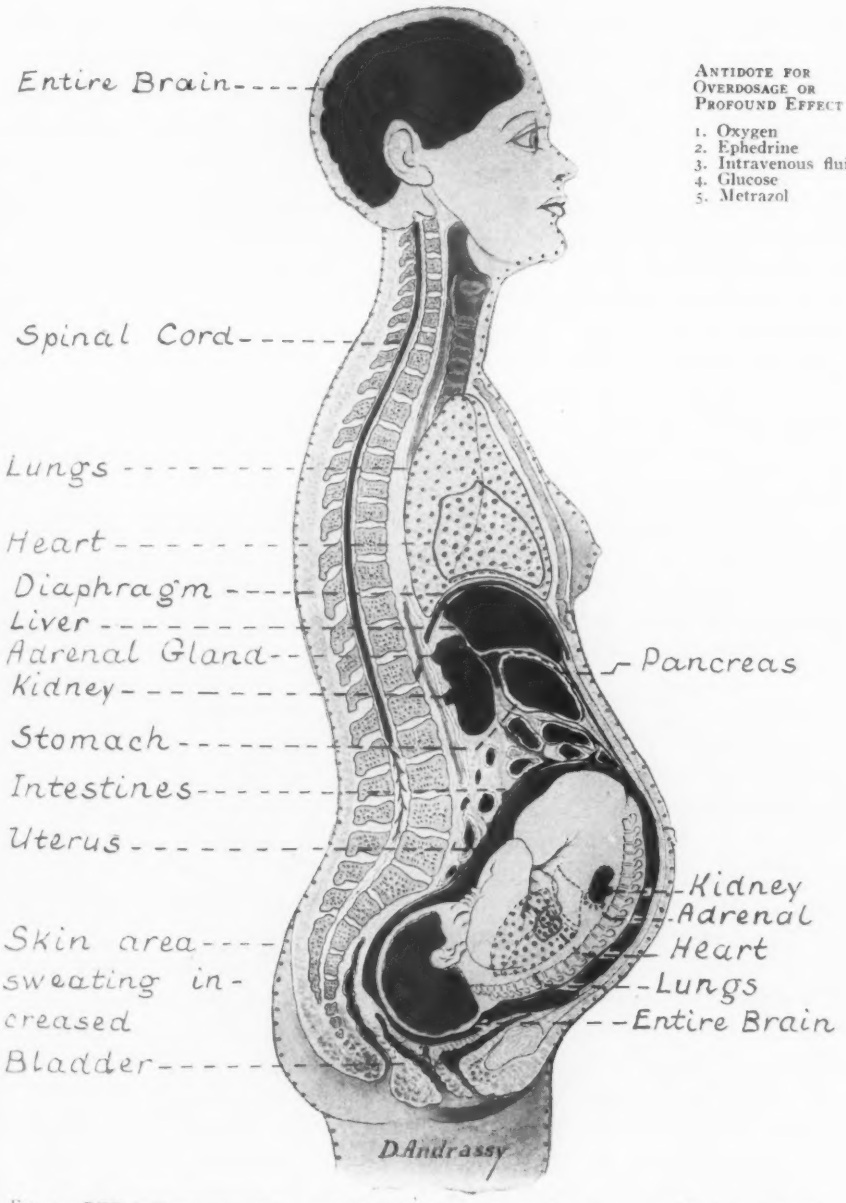
ANTIDOTE FOR OVERDOSAGE OF PROFOUND EFFECT

1. Oxygen
2. Spinal drainage fluid
3. Vasopressor drugs
4. Intravenous fluids
5. Gravity autotransfusion

FIG. 2.—RED indicates stimulation and BLUE indicates depression of maternal and fetal organs. Solid color indicates intensified action, Dotted color indicates moderate action, and Outline dots indicate minimal action. Numbers (1 and 2) on ascending and descending arrows indicate sequence of stimulation and depression.

—From "Control of Pain in Childbirth," by Clifford A. Lull, M.D. and Robert A. Hingson, M.D., J. B. Lippincott Company, Philadelphia, Pa.

ETHYL ETHER



ANTIDOTE FOR OVERDOSAGE OR PROFOUND EFFECT

1. Oxygen
2. Ephedrine
3. Intravenous fluids
4. Glucose
5. Metrazol

FIG. 3.—RED indicates stimulation and BLUE indicates depression of maternal and fetal organs. Solid color indicates intensified action, Dotted color indicates moderate action, and Outline dots indicate minimal action. Numbers (1 and 2) on ascending and descending arrows indicate sequence of stimulation and depression.

—*From "Control of Pain in Childbirth," by Clifford A. Lull, M.D. and Robert A. Hingson, M.D., J. B. Lippincott Company, Philadelphia, Pa.*

dislodgment of the needle from the subarachnoid space. Six cases or 12 per cent required inhalation anesthesia for delivery. Included in this group are the two complete failures previously mentioned, one patient who experienced pain during the decomposition and extraction of the second of twins, and the three cases in whom the needle was dislodged (in two of these the episiotomy was repaired without supplementary anesthesia).

EFFECT ON LABOR

It is impossible to analyze accurately the effect on the duration of labor in a series this small. It is our impression that labor is not lengthened if certain prerequisites are observed. The patient must be in active labor and have reached a point where she is suffering severe pain, not merely the discomfort of early first-stage labor. The presenting part should be engaged and on a level with the ischial spines. This applies equally to multipara as well as nullipara. The cervix should be effaced and 4 cm. dilated before instituting the method in nullipara. Dilatation of 2 cm. is satisfactory for multiparous patients. Failure to observe these rules will invariably result in prolongation or even cessation of labor.

In no case did we observe any interference with either the frequency or force of uterine contractions. Furthermore, we were impressed by the apparent acceleration of cervical dilatation. This would seem to at least suggest that under proper conditions the first stage of labor is shortened by this method. While the mechanism of the first stage of labor is not appreciably altered, it must be frankly admitted that the normal mechanism of the second stage is in most instances delayed. One patient delivered spontaneously, in the remaining 49 operative delivery was necessary or an incidence of 98 per cent. Forty-three cases or 86 per cent were delivered by low forceps, six cases or 12 per cent were delivered by mid-forceps. Every instance of mid-forceps application occurred in occiput posterior positions.

It is our impression that mid-forceps is the rule in occiput posterior positions in continuous spinal anesthesia because the relaxed pelvic floor permits extension of the head with resultant arrest.

In all fairness, it should be stated that despite the high incidence of forceps delivery, these were greatly facilitated by the complete pelvic relaxation which was obtained. For example, no sulcus tears were encountered in the mid-forceps group. We do not believe this statement can be made in cases delivered under inhalation anesthesia. Furthermore, with proper application of forceps and episiotomy, normal pelvic anatomy should be preserved. We were unable to note any deviation from the normal third-stage mechanism. In all instances the placenta separated completely and promptly (usually within three minutes) and was expressed by the simple procedure of traction and fundal pressure. No case of retained placenta occurred.

While the blood loss was not measured, we believe that we may state with accuracy that it was less than normal, *i.e.*, less than 250 cc. In no case did the uterus fail to contract firmly at the end of the third stage, thus

precluding the necessity for the routine use of oxytoxics. We do not advise the administration of either pituitrin or any ergot derivative until termination of the third stage. Failure to observe this precaution may result in retained placenta.

EFFECT ON THE MOTHER

Ninety per cent of the mothers reacted favorably to this method and were enthusiastic over the dramatic relief of pain. Approximately 10 per cent, mainly multipara, were either emotionally or intellectually unsuitable for continuous spinal anesthesia. While their behavior was entirely satisfactory during labor, it was difficult to convince them upon arrival in the delivery room that they would experience no pain during the actual birth of the child. There were no instances of broken needles. Infections, severe circulatory collapse or sensitivity to the various drugs were not encountered. In a few cases primary unilateral anesthesia occurred. This was easily overcome by additional dosage and placing the patient on the opposite side. Little or no alteration of blood pressure occurred in the vast majority of cases. In only three patients did the blood pressure drop to a serious level. Rapid restoration was effected by the administration of oxygen, a vasoconstrictor drug and elevation of the lower extremities to a 90 degree angle. Twelve per cent of the group were hypertensive because of toxemia. In each instance the blood pressure was lowered and the urinary output increased under continuous spinal anesthesia.

One patient developed postpartum eclampsia. She was admitted to the hospital in labor complicated by severe toxemia, her blood pressure being 180/120. During ten hours of spinal anesthesia the blood pressure dropped to 140/100 and the urinary output was 1200 cc. (Spinal was instituted early to observe its effect in severe toxemia). It is our belief that the single convulsion which followed did not result from the anesthesia.

Twenty-two cases, or 42 per cent, experienced rather severe but transient headache which was relieved by mild analgesics. This complication could be prevented in most instances by having the patient remain in the supine position without a pillow for 48 hours postpartum. There were no instances of backache or pain in the legs during the postpartum period. Twelve cases or 24 per cent had urinary retention following delivery. All of these were transient, disappearing by the end of 72 hours. This incidence is no higher in our experience than with other anesthetics. Maternal morbidity in our series was 6 per cent. There were no maternal deaths.

EFFECT ON THE INFANT

Spinal and continuous spinal anesthesia have no adverse effect upon the foetus. The illustrative charts reproduced here show the comparative effect on both mother and child of spinal anesthesia and ethyl ether. The marked contrast between the two graphically demonstrates the superiority of spinal anesthesia. Dr. Kenneth A. Heard of the University of Toronto has stated: "He who denies the baby the safety of spinal anesthesia, must be prepared

to accept the responsibility for its protection from ether." There were 51 live babies in this series and no stillbirths. Respiration was spontaneous and immediate and all infants cried lustily. Cyanosis did not occur in a single case. One infant died 72 hours postpartum. This occurred in a seven months premature and in our opinion can not be attributed to the anesthesia.

INDICATIONS AND CONTRAINDICATIONS

Although our series is small and our experience with this method limited, we feel that continuous fractional spinal anesthesia is especially indicated in the following conditions: (1) prematurity; (2) some cases of heart disease; (3) hypertensive toxemia; (4) pulmonary disease, such as tuberculosis; (5) previous cervical and vaginal repair because of its relaxing effect on the lower uterine segment, pelvic floor and perineum.

Contraindications may be divided into local, general and obstetric. The local contraindications are: (1) deformity of the spine or disease of the spinal cord; (2) local infections at or near the site of injection. The general contraindications are: (1) marked obesity; (2) history of sensitivity to the drug; (3) those emotionally unsuited; (4) severe anemia.

The obstetrical contraindications are: (1) nonengagement of the presenting part; (2) cephalopelvic disproportion; (3) known fetal deformity or dead baby; (4) placenta previa; (5) internal podalic version.

COMMENT

Continuous spinal anesthesia for labor and vaginal delivery is still in the experimental stage. We urge extreme caution in its use. It should only be employed either in the hands or under the direction of one completely familiar with the technic and in a well equipped institution. All precautions to safeguard the patient's welfare should be taken. Oxygen, vasoconstrictor drugs, stimulants and intravenous fluids should be immediately available at all times. Because of the high incidence of operative delivery, continuous spinal anesthesia should not be attempted by the untrained obstetrician. The method is time-consuming and requires constant personal supervision. It is both unfair and dangerous to give the initial injection and then place the responsibility for its continuation in the hands of an intern or nurse. We feel that continuous spinal anesthesia affords the patient the additional safety factor of withdrawal of the anesthetic agent should any untoward effect occur. This is in contrast to caudal or single injection spinal in which this is impossible.

SUMMARY

1. Fifty cases of continuous fractional spinal anesthesia for labor and delivery are presented and discussed.

2. Comparison between the various drugs seems to indicate the superiority of 1.5 per cent metycaine in Ringer's solution.

3. It has been shown that the most favorable site of injection is the first or second lumbar interspace.

4. Premature institution of the method invariably results in prolongation or cessation of labor.

5. The patient should be in active labor with the presenting part in mid pelvis and the cervix 2 to 4 cm. dilated, depending upon the parity.

6. The progress of the first stage is apparently accelerated.

7. The second stage of labor is altered, and the incidence of operative delivery is greatly incerased.

8. The third stage of labor proceeds normally, and the blood loss is minimal.

9. This anesthesia is without adverse effect on the baby.

10. We do not advocate this method as a routine procedure and urge caution in its employment. While no serious complications occurred in this series, further trial is necessary to evaluate its future place in obstetrical anesthesia.

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THE USE OF THIOURACIL IN THE PREPARATION OF PATIENTS WITH HYPERTHYROIDISM FOR THYROIDECTOMY*

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THE PREPARATION of thyrotoxic patients for thyroidectomy has undergone a gradual evolution based on the use of physical or chemical agents intended to correct the underlying physiologic abnormality and bring the patient to surgery in as nearly normal a state as possible. Bed rest alone, with adequate sedation, accomplished a minimal but significant change in this direction. The introduction of the use of iodine for this purpose by Plummer,[1] in 1923, marked a signal advance, with a resultant lowering of operative morbidity and mortality.

During the "iodine period" of thyroid surgery in the years which intervene from Plummer's contribution until the present, refinements in surgical technic with modification of the one-stage subtotal thyroidectomy have been superimposed on iodine treatment with a view to more adequate preparation for the final removal of the gland. Pole ligation and staged thyroidectomy, employing various technics and intervals, have found a useful place in occasional cases. However, the fundamental problem remained of a patient undergoing operation suffering from a metabolic abnormality greatly aggravated by the physiologic stress and local manipulation incident to thyroidectomy. Attempts to reduce the importance of these latter factors by variation in anesthetic agents have led to the use of a number of anesthetic and operative technics which only ameliorate but do not solve the problem.

In 1941 and 1942[2, 3] the MacKenzies and McCollum reported that sulfanilylguanidine produced goiters and depressed the basal rate of oxygen consumption in experimental animals. Richter and Clisby[4] made similar observations using thiocarbamide. These observations formed the basis for the use of an entirely new series of chemical agents possessing potent but at that time poorly understood action on the thyroid gland.

Astwood[5] studied a number of these goitrogenic agents and determined that

* Aided in part by a grant from the Josiah Macy, Jr. Foundation.

2-thiouracil was among the most effective and that unlike goitrogens of the thiocyanate group the hyperplastic effect on the gland was not abolished by the coincident administration of iodine. To Astwood, also, belongs the credit for first using agents of this class in the treatment of thyrotoxicosis; his work with thiouracil led to our employment of the drug as a means of preparing thyrotoxic patients for surgery. Himsworth[6] has confirmed these observations in a series of patients treated with thiouracil; one of the six patients studied by him was operated upon.

In 1942 and 1943, the goitrogenic action of thiocyanate was investigated by members of the Thyroid Clinic of the Massachusetts General Hospital. Observations of thiocyanate goiter in man[7] had led Dr. E. M. Chapman[8] to attempt the use of thiocyanate as a means of altering the thyroid function of four patients with thyrotoxicosis. The results were not encouraging, however, and only one of the four patients treated showed a lowering of basal metabolic rate. Therefore, with the knowledge of Astwood's work, attention was shifted to thiouracil.

The ideal preparative drug for thyroidectomy would be one which so modified the underlying metabolic abnormality as to bring the patient to the surgeon with no evidence of thyrotoxicosis, allowing him to remove the gland and produce permanent relief without subjecting the patient to the hazards of surgery while thyrotoxic. It has been our purpose to ascertain to what degree thiouracil approached this ideal. The complications of thyroidectomy fall into three groups: those related to surgery in general, such as hemorrhage and sepsis; those related to the peculiar anatomical relationships of the thyroid gland, such as nerve or parathyroid injury; and, third, those which stem from the pathologic physiology of thyrotoxicosis, chiefly storm and postoperative thermal reactions. It has been our hope that thiouracil would lessen the hazards in the third group of complications. However, in focusing our attention upon those factors we must not lose sight of possible increased hazards in the first two categories traceable to increased vascularity or friability of the gland.

Thiouracil is a stable organic compound related to thiourea. It is administered by mouth in the form of a 0.1 Gm. tablet, and is well tolerated by the patient with thyrotoxicosis.* Toxic by-effects have been observed in occasional cases and will be discussed below; these evidences of toxicity resemble sulfonamide sensitivity, and the same type of precautions should be taken in using thiouracil that one would employ with sulfonamides.

On June 24, 1943, our first thiouracil-treated patient was operated upon, and since that time 53 patients have received the drug as a preoperative measure. Several of these patients received the drug for such a short time as to render observations on its action of little meaning; others were not on the drug at the time of operation or have been followed for too short a time to permit valid conclusions to be drawn. In all, 34 patients have been treated preoperatively, have come to operation on thiouracil, and have been followed long enough to form the basis of this report.

* The thiouracil used in this study has been supplied through the kindness of Dr. B. W. Carey of the Lederle Laboratories, Inc.

CLINICAL DATA

The patients included in this report were seen and diagnosed as having hyperthyroidism by members of the Thyroid Clinic of the Massachusetts General Hospital and by the house and visiting staffs on the wards. The patients prepared for operation with thiouracil were kept in the hospital throughout the period of preoperative treatment. Their response to treatment was followed by basal metabolic rates measured at least twice a week and by the clinical observation of members of the Thyroid Clinic. Unless stated otherwise, the daily dose of thiouracil was 0.6 Gm., usually administered as 0.2 Gm. in three doses. The drug was not started until after a satisfactory base line in basal metabolic rate had been obtained. The drug was stopped on the day of operation. The patients were released from the hospital postoperatively without any medication and are being followed in the Thyroid Clinic.

Eight of our patients had been treated with potassium iodide before thiouracil was started. One continued to take the potassium iodide during the time of treatment with thiouracil. Seven patients had received some form of iodide therapy until 10 to 30 days before starting treatment with thiouracil. They did not receive any further iodine. The remaining 26 patients were previously untreated cases; none of them had received any specific drug therapy for thyrotoxicosis, and thiouracil was the only drug used to alter thyroid function preoperatively.

The patients studied in this series were operated upon by eleven surgeons. Four of the surgeons performed these operations while resident on a surgical service, accounting for 25 of the 34 cases. The remaining nine cases were operated upon by seven members of the visiting staff.* Unless otherwise specified, the operation performed was a one-stage subtotal thyroidectomy employing section of the strap muscles and hemostasis with fine nonabsorbable suture material (silk or cotton). Drainage for 18 to 24 hours with a small midline or lateral drain was used in several of the cases; it is not routine. The postoperative regimen employs an oxygen tent, intravenous glucose and thiamine, single room and special nurse on all cases. The general handling of the patients follows closely the outline of Cope and Welch.[9]

As a control series, 35 thyroidectomies for thyrotoxicosis, performed at the Massachusetts General Hospital in the years 1941 and 1942, have been selected. These iodine-treated control cases were all operated upon between the months of June and December of their respective years, these being the months during which the thiouracil cases were operated upon in 1943. The distribution of initial B. M. R. levels in this control group of cases coincides closely with that of the thiouracil-treated group. Thus, the 1941 and 1942 iodine-treated cases used here constitute an adequate control group, presenting problems of similar magnitude in their surgical care. These cases, like the thiouracil-treated

*We are indebted to Dr. A. W. Allen, Chief, East Surgical Service; Dr. L. S. McKittrick, Chief, West Surgical Service; Dr. J. V. Meigs, Chief, Gynecologic Service; Dr. R. R. Linton, Dr. R. H. Smithwick, and Dr. G. A. Donaldson for data on cases operated upon by them.

I. PATIENTS PREPARED FOR OPERATION WITH THIOURACIL ONLY

A—Diffuse Hyperplasia (23 Patients)

Patient. No.	Age	Sex	Symptoms and Duration	Initial B.M.R. Level	Length of Thio-uracil Treatment	Pre-operative Level	Oper-tion	Anes-thetic	Nature of Gland	Postoper. Thermal Response	Follow-up Data	Remarks
S. M. 23895	42	M	Weakness—5 mos.	+45	32 days	+5	6.24.43	G-O-E	Very vascular—not friable	T. 102° Next day	10 mos. −15	
M. B. 24033	34	F	Palpitation—1 yr. Goiter—1 yr. Exophthalmos +	+30	16 days	+7	7.15.43	G-O-E	Very vascular and friable	Smooth	3 mos. −10	
E. K. 24085	20	F	Nervous—3 mos. Goiter—2 mos.	+38	10 days	+2	7.26.43	G-O-E	Very vascular and friable	T. 104° 1st day	5 mos. −11	Operation made more difficult by physical characteristics of gland.
J. S. 24049	30	F	Wt. loss—3 mos.	+40	17 days	+15	7.31.43	G-O-E	Firm—not very vascular	Smooth	5 mos. +15	
J. W. 24168	61	M	Weakness—6 mos. Exophthalmos ++	+20	19 days	±0	9. 9.43	Cyclo-propane	Vascular—not friable	T. 102° 1st day	5 mos. −8	
R. R. 24218	18	M	Fatigue—7 mos. Army rejection	+50	17 days	+22	9.22.43	G-O-E	Soft—hard to handle	Smooth	9 mos. +3	Operated upon prematurely with rate at +22. Preliminary biopsy.
B. B. 422660	53	F	Wt. loss—4 mos. Exophthalmos ++	+28	17 days	±0	10.22.43	G-O-E	Vascular but firm	Smooth	4 mos. −24	Preliminary biopsy.
M. M. 24227	40	M	Wt. loss—4 mos.	+35	11 days	+10	11. 2.43	G-O-E	Soft—not very vascular	T. 101° 1st day	3½ mos. −26	Preliminary biopsy.
F. P. 24282	21	F	Palpitation—1 mo. Goiter—1 mo.	+35	17 days (40 days	±0 −15)	11. 8.43	G-O-E	Soft—not vascular	T. 101°	4 mos. +1	Operation postponed because of dental infection; rate then came down to myxedema levels.

24218			Army rejection									rate at +22. Preliminary biopsy.
B. B. 422660	53	F	Wt. loss—4 mos. Exophthalmos ++	+28	17 days	±0	10.22.43	G-O-E	Vascular but firm	Smooth	4 mos. −24	Preliminary biopsy.
M. M. 24227	40	M	Wt. loss—4 mos.	+35	11 days	+10	11. 2.43	G-O-E	Soft—not very vascular	T. 101° 1st day	3½ mos. −26	Preliminary biopsy.
F. P. 24282	21	F	Palpitation—1 mo. Goiter—1 mo.	+35	17 days (40 days	±0 −15)	11. 8.43	G-O-E	Soft—not vascular	T. 101°	4 mos. +1	Operation postponed because of dental infection; rate then came down to myxedema levels.
F. D. 24336	29	F	Nervous—8 mos. Goiter—2½ mos.	+60	20 days	+7	11.16.43	G-O-E	Soft—not friable	T. 101.8° 1st day	3 mos. −13	Preliminary biopsy.
L. O'B. 24298	24	F	Nervous—7 mos. Diarrhea—6 mos.	+35	13 days	+3	12. 6.43	G-O-E	Firm—not vascular	T. 100° 3 days	5 mos. −10	
J. R. 24469	53	F	Pain rt. eye—9 mos. Exophthalmos +++	+45	41 days	+17	1.17.44	G-O-E	Not vascular	Smooth	4 mos. −13	Unilateral (right) exophthalmos; not made worse by operation.
M. G. 24472	35	F	Wt. loss—12 mos.	+25	15 days	±0	1.21.44	G-O-E	Satisfactory	Smooth	2 mos. −25	
L. A. 24361	42	F	Nervous—2 yrs. Goiter—1 yr.	+45	9 days (30 days	+5 −2)	11.22.43	G-O-E	Firm—not vascular	T. 100° 3rd day	3 mos. −26	Preliminary biopsy.
B. S. 21955	45	F	Heat intolerance—3 yrs. Treated with x-ray +KI	+35	24 days	+2	1.21.44	G-O-E	Satisfactory	Smooth	3 mos. −7	Off iodine for 3 months before thiouracil started.
A. B. 15207	32	F	Wt. loss—9 mos. Thyroidectomies 1936—1941	+45	11 weeks	+1	1.22.44	G-O-E	Friable—easy bleeding	Smooth	2 mos. +20	Recurrent thyrotoxicosis following 2 operations at outside hospital; treated in Out-Patient Dept. for 1st 2 months of thiouracil therapy.
J. C. 24531	40	M	Nervous—1 yr. Wt. loss—1 yr.	+45	31 days	−8	2:24.44	G-O-E	Satisfactory	T. 103° 1st day	2 mos. −12	*Staph. aureus* wound sepsis.
A. K. 440001	45	F	Wt. loss—1 yr. Hypertension	+45	24 days	+15	4. 4.44	G-O-E	Satisfactory	Smooth		Had subsequent lumbodorsal sympathectomy; found to have adenocarcinomatous nodule in gland.
R. W.*	25	M	Wt. loss—16 mos.	+65	26 days	+9	4.18.44	G-O-E	Satisfactory	Smooth		Remarkably dry gland in view of histologic hyperplasia.
K. G. 24613	33	F	1941—Hemi-thyroidectomy Nervous—3 mos.	+35	45 days	−12	4.20:44	G-O-E	Very vascular and friable	T. 102° 1st day	1 mo. −3	Recurrent thyrotoxicosis; had remaining lobe removed; thyroid also used in preparation. Surgically difficult to handle. Transient tetany.
D. F. 24727	27	F	Nervous and tired 9 mos.	+45	12 days (42 days	+5 +1)	4:24:44	G-O-E	Satisfactory	Smooth		Operation postponed because of throat infection. Thiouracil cut to 0.2 Gm. per day for last 24 days of treatment.
D. M. 24787	34	F	Goiter—2 mos.	+35	17 days	+4	5: 3.44	G-O-E	Extremely vascular	Smooth	1 mo. −22	Concomitant treatment with thyroid gr. 1.5 per day did not reduce vascularity.
S. K. 24778	39	F	Nervous—6 mos. Tremor—6 mos.	+45	35 days	+1	5:16.44	G-O-E	Vascular but not friable	Smooth	1 mo. +7	

B—With Long-standing Nodular Goiters (3 Patients)

R. S. 24170	48	F	Goiter—5 yrs. Nervous—17 mos.	+40	14 days	+20	10. 1.43	G-O-E	Firm but vascular	Smooth	6 mos. +20	Questionable residual thyrotoxicosis.
M. B. 24180	49	F	Goiter—15 yrs. Nervous—6 mos.	+20	20 days	±7	10.20.43	G-O-E	Involuted—firm	Auricular fibrillation	5 mos. −7	Large retrosternal goiter.
F. R. 24724	43	F	Goiter—3 yrs. Palpitation—3 mos.	+28	18 days	+6	4.29.44	G-O-E	Involuted	Smooth	2 wks. −10	Concomitant rheumatic heart disease, with mitral stenosis and auricular fibrillation. Did very well postoperatively.

II. PATIENTS PREVIOUSLY IODINIZED PREPARED FOR OPERATION WITH THIOURACIL AFTER STOPPING IODINE TREATMENT (7 PATIENTS)

A. S. 23905	51	F	Palpitation—2 yrs. Iodine—6 mos.	+30	19 days	+16	9.10:43	G-O-E	Well involuted—firm	T. 102° 1st day	6 mos. +9	
W. L. 24260	18	M	Wt. loss—5 mos. Taking iodine—1 mo. Disch. from Navy	+40	29 days	+12	10.20:43	G-O-E	Soft—friable hemorrhagic	T. 103° 3 days	2 mos. +11	Preliminary biopsy.
B. K. 24323	39	F	Nervous—15 mos. Goiter—15 mos. On iodine—1 yr.	+35	27 days	−8	10.25.43 12. 7.43	G-O-E G-O-E	Soft—not smooth friable	Smooth	5 mos. −26	Done in two hemithyroidectomies. Prepared for first side with iodine.
K. T. 23890	39	M	Soreness of eyes—10 mos. Wt. loss—4 mos. On iodine 1½ yrs. Exophthalmos ++++	+30	14 days	+5	1. 6.44	G-O-E	Firm—not vascular	T. 101° 1st day	3 mos. +7	Severe ophthalmopathy, not made worse by thiouracil or operation. On thyroid gr. 3 a day for 4 months.
M. S. 23309	19	F	Nervous—18 mos. On iodine—3 mos.	+50	35 days	+2	1.12.44 1.28.44	G-O-E G-O-E	Soft—not friable	Smooth	4 mos. −31	Done in two hemithyroidectomies. Prepared for first side with iodine.
G. W. 24637	52	F	Weakness—8 mos. Iodine—8 mos.	+55	35 days	−8	4. 7.44	G-O-E	Firm—vascular	T. 101° 1st day	2 mos. −5	Transient tetany.
H. M. 24904	46	F	Dyspnea—7 mos. Iodine—5 mos.	+25	20 days	+2	4.17.44	G-O-E	Firm—not vascular	Smooth	2 mos. −5	

III. PATIENTS PREPARED FOR OPERATION WITH IODINE AND THIOURACIL (1 PATIENT)

C. A. 23795	28	M	Nervous—2 yrs. On iodine—3 mos. Exophthalmos +++	+25	31 days	+20	6.12:43	Local	Firm	Smooth	9 mos. +23	Preliminary pole ligation. Very minimal lowering of rate by thiouracil—iodine given simultaneously.

* Patient of Dr. L. S. McKittrick, Palmer Memorial Hospital.

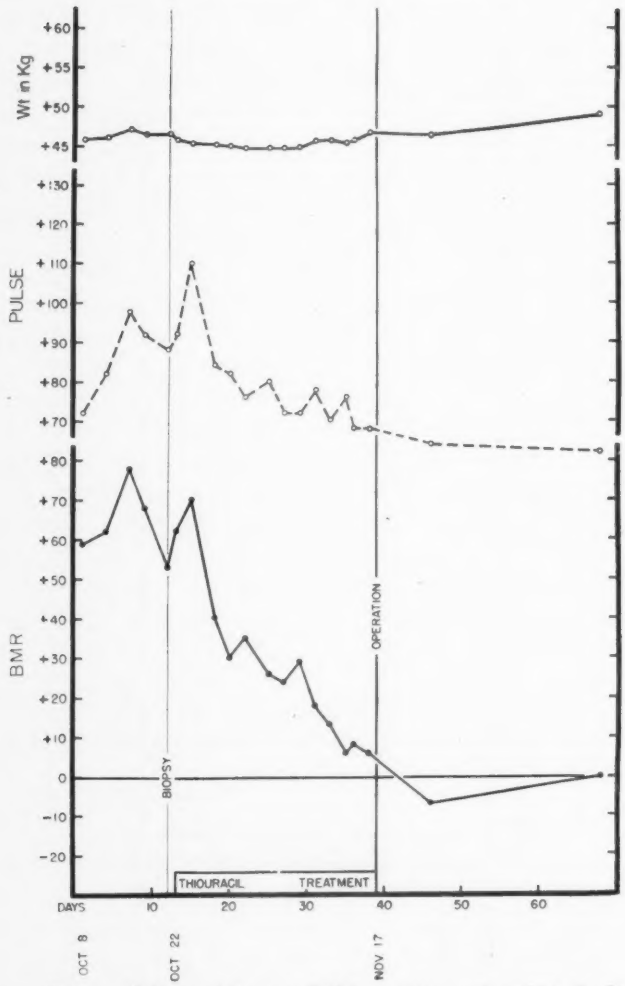


FIG. 1.—Pulse, weight and B.M.R. responses of patient F. D. (No. 24336) to thiouracil treatment; a previously untreated case of hyperthyroidism with an initial B.M.R. "level" of +60. The drug was started following biopsy of the gland. The rate rapidly fell to the neighborhood of +5, at which point subtotal thyroidectomy was performed. The pulse response is striking. There was no significant weight-gain in this case. The histologic appearance of the thyroid at biopsy and at thyroidectomy is shown in Figure 8.

patients, were operated upon in the great majority of instances by the surgical residents. The postoperative handling was identical with the exception of the fact that the thiouracil cases received no postoperative iodine.

The clinical response to thiouracil was satisfactory in all of our patients. The patients experienced improved tolerance for the heat, decreased nervousness, and increased strength usually within ten days of starting the drug. The tremor was observed to decrease and to disappear in several cases, and the pulse rates became nearly normal. The weight curves were variable.

The thyroid glands did not appear to become larger; nor did they become firmer, as one usually observes in the thyrotoxic patient treated with iodine.

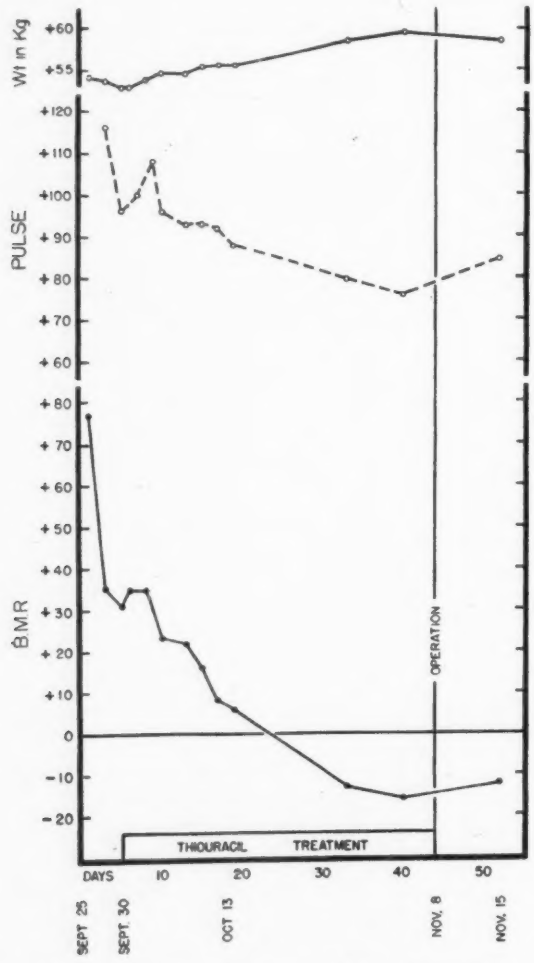


FIG. 2.—Pulse, weight, and B.M.R. responses of patient F. P. (No. 24282) to thiouracil treatment. With an initial B.M.R. of +78, settling down on bed rest to a "level" of +35, this patient's B.M.R. fell to +0 in 17 days of treatment. Further treatment was necessitated by the appearance of dental sepsis which postponed operation; in a total of 40 days of treatment the B.M.R. fell to −16 and the patient became clinically myxedematous (compare with histologic sections shown in Figure 11).

Indeed, in a few cases the thyroid became softer. This change in consistency gave the impression in some instances that the gland became smaller. A bruit and thrill appeared over the thyroid in several cases. In no instance did a preexisting bruit disappear during treatment with thiouracil. In some patients the bruit became louder, an observation which correlates with the vascularity observed at operation and seen on microscopic section.

THE PREOPERATIVE BASAL METABOLIC RESPONSE

The basal metabolic response to thiouracil is signalized by the fact that it is evidently possible to bring the rate down to between 0 and +10, regardless

of the initial values, providing one maintains treatment with the drug for an adequate period of time.

The initial fall in basal metabolic rate in the cases treated with thiouracil alone is similar to the iodine response curves reported by Means and Lerman.[10] In contrast to the iodine response curves which level off after an initial drop the thiouracil response curves continue their descent until a myxedema level is approached. A series of curves showing the metabolic response to thiouracil is presented in the paper by Rawson, *et al.*,[11] reporting the metabolic studies with thiouracil carried out in this clinic.

The basal metabolic responses seem to fall into two groups: In the patient with untreated thyrotoxicosis, having an initial basal metabolic rate in the higher range and with diffuse hyperplasia, the response to thiouracil is usually rapid and the fall to a normal metabolic rate may take place within ten days to three weeks. Examples of this type of response are shown in Figures 1 and 2.

Patients treated with iodine before thiouracil therapy constituted a second group. The fall in the basal metabolic rates of these iodinized patients was delayed as compared with the fall noted in the basal metabolic rates of previously untreated cases, requiring from four to six weeks to reach normal.

One patient who was fully iodinized was treated for a month with thiouracil, continuing iodine during this period. The response to this therapeutic combination was minimal and during the month in question his rate did not significantly depart from a level of +20. We realize, in the light of subsequent experience, that the response would have been more rapid had iodine treatment been discontinued; or, conversely, had we elected to continue iodine, we should have been content to wait two or three months for the thiouracil response.*

Two patients who had had large goiters for many years and had only recently developed symptoms of thyrotoxicosis were also slow in their response to thiouracil. The histologic appearance of their thyroids was that of involution with secondary hyperplasia. Clinically and histologically, they tend to fall in the same group as those patients who had received iodine treatment before thiouracil was started. An example of this group is shown in Figure 3.

It is our conviction at the present time that if thiouracil is continued, however, even in this group of iodine treated patients or patients with old nodular goiters recently become toxic, ultimately a complete metabolic response will be obtained. During the course of our work we were not aware of this fact in some of the earlier cases and doubtless operated upon them prematurely from the standpoint of the basal metabolic response.

In Table I are shown the essential data on all the operated cases, divided into groups according to their status with respect to iodine therapy.

COMPARISON WITH IODINE-TREATED CASES

Any attempt to evaluate thiouracil preparation must involve a comparison with the previous method of preparation which it may replace. In an effort

*A patient who did not come to operation on thiouracil because of a failure to demonstrate a metabolic response to the drug during six weeks of treatment with both thiouracil and iodine also demonstrates this point.

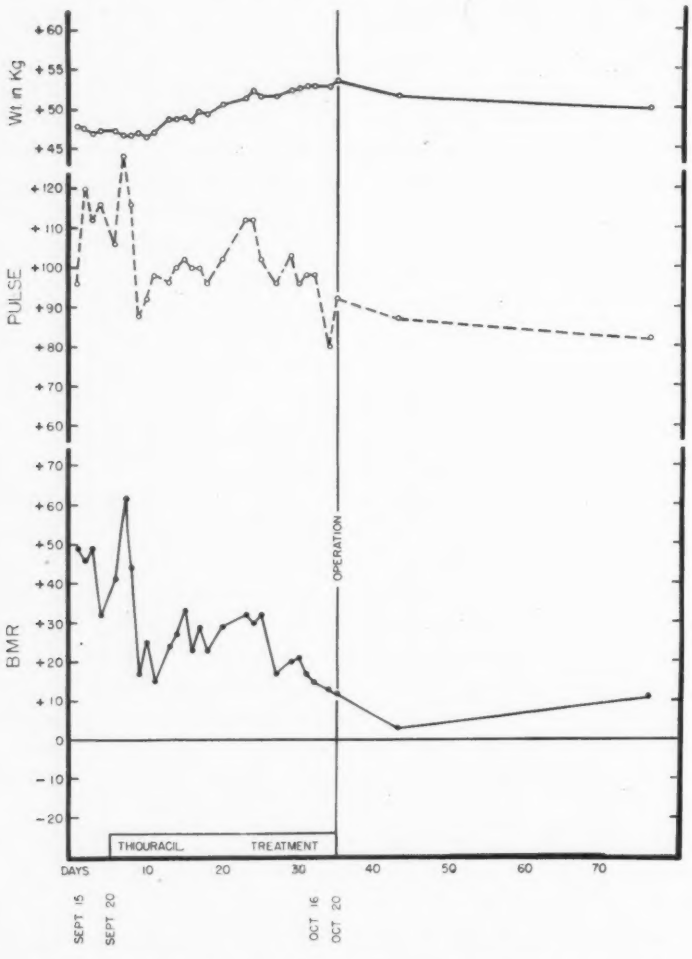


FIG. 3.—Pulse, weight, and B.M.R. responses to thiouracil of a patient (M. B. No. 24180) with a long-standing colloid goiter recently become toxic. Treatment for 30 days did not alter markedly the trend of the B.M.R. In retrospect, we realize that this patient was operated upon prematurely, and that another 10 or 15 days of treatment might have sufficed to reduce the rate to normal. Compare with histologic sections (Figure 13).

to accomplish this, 35 thyroidectomies performed with iodine preparation have been analyzed with respect to their preoperative metabolic response and postoperative course.

The preoperative metabolic response to thiouracil differs strikingly from iodine preparation in one important regard which it is difficult to overemphasize. This difference resides in the fact that a group of iodine-treated cases show a shift downwards in their metabolic rate, averaging about 25 points, whereas thiouracil treatment shifts the distribution of metabolic rates from the same starting figure to the region of ±0, a drop of almost 50 points.

As shown in Figure 4, the iodine-treated patients show a shift in the peak distribution from a B. M. R. of +45 to a B. M. R. of +20, but there is a very considerable spread, with some of the patients after iodine therapy still main-

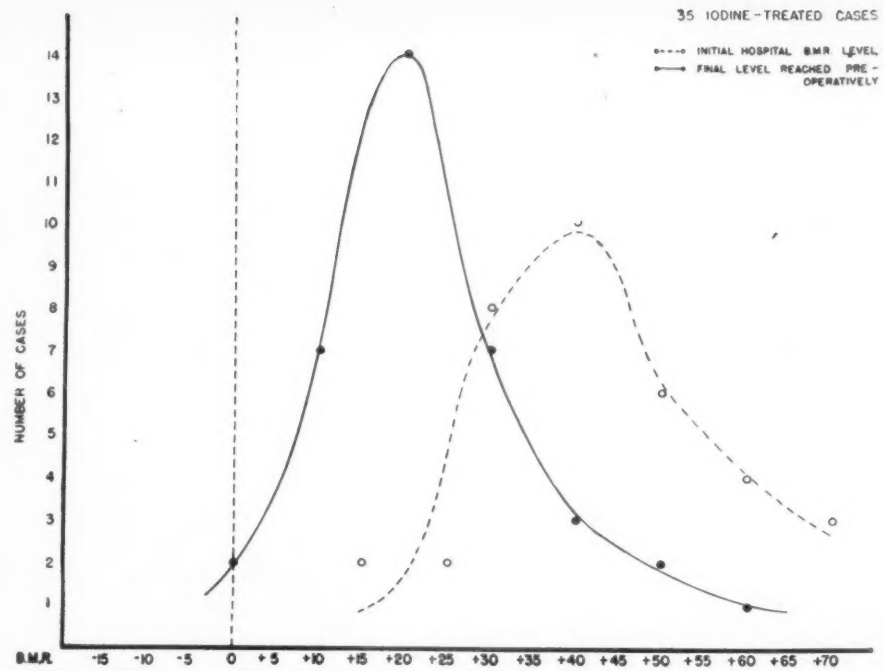

35 IODINE-TREATED CASES
INITIAL HOSPITAL B.M.R. LEVEL
FINAL LEVEL REACHED PRE-OPERATIVELY
NUMBER OF CASES
B.M.R.
-15 -10 -5 0 +5 +10 +15 +20 +25 +30 +35 +40 +45 +50 +55 +60 +65 +70

FIG. 4.—Change in distribution curve of basal metabolic rates in 35 thyrotoxic patients prepared for operation by the administration of iodine. There is a shift in the peak from + 40 to + 20; there is still quite a wide spread in the B.M.R. values after iodine therapy.

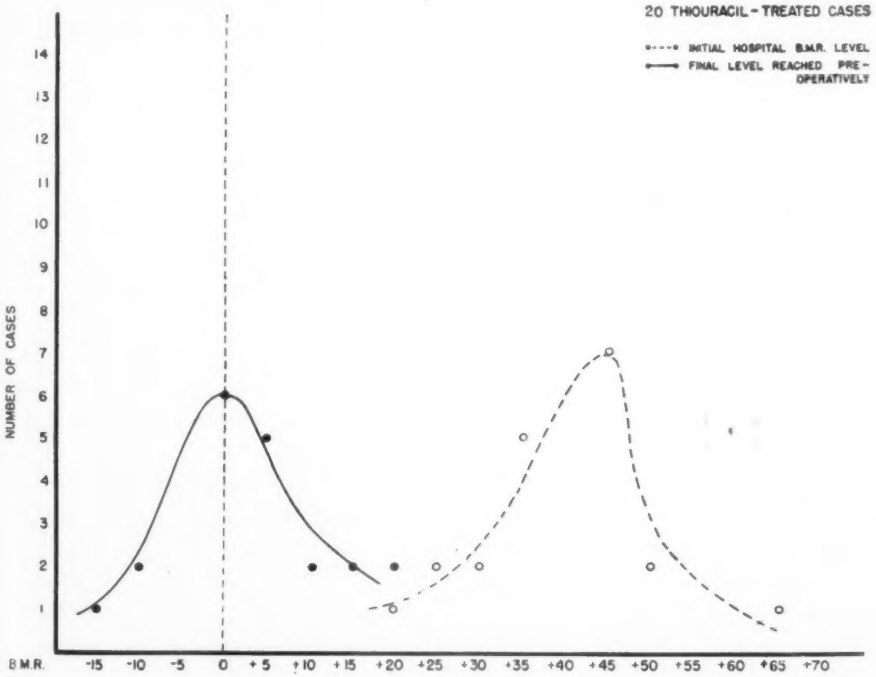

20 THIOURACIL-TREATED CASES
INITIAL HOSPITAL B.M.R. LEVEL
FINAL LEVEL REACHED PRE-OPERATIVELY
NUMBER OF CASES
B.M.R.
-15 -10 -5 0 +5 +10 +15 +20 +25 +30 +35 +40 +45 +50 +55 +60 +65 +70

FIG. 5.—Change in distribution curve of basal metabolic rates in 20 thyrotoxic patients prepared for operation with thiouracil. The peak distribution is shifted from + 45 to + 0; there is a narrow spread in the B.M.R. values after thiouracil therapy.

taining a B. M. R. in the higher level, with others falling quite low. On the other hand, as shown in Figure 5, the thiouracil group show a shift in peak from +45 to ±0, and the cases are rather closely grouped between 0 and +10 at the preoperative determination. Stated otherwise, thiouracil, if correctly used, can be relied upon to bring the patient's metabolic rate to or near 0 before operation. The iodine response curves of Means and Lerman[10] demonstrate that with a peak distribution of initial B. M. R.'s at +40 one will naturally expect the level to be +20 after iodine therapy. Furthermore, we know from experience that if the iodine is continued on for another two or three weeks, the level will usually not fall much lower. With thiouracil the level will continue to fall until it reaches ±0 or lower.

It is probable that continuance of thiouracil over a period of months will produce myxedema in thyrotoxicosis; two thyrotoxic patients treated by us have been allowed to fall to levels in the vicinity of —15 before operation. Furthermore, we know from one case seen in this clinic that thiouracil given in adequate doses over a period of months can produce a large goiter and clinical myxedema in a nonthyrotoxic patient. In the surgical cases, operation has usually been performed with the rate in the vicinity of 0 to +10, at which time the drug has been stopped.

For those clinicians who feel that an iodine "escape" phenomenon may occasionally complicate prolonged preoperative iodine treatment, thiouracil has the advantage that long-continued treatment serves always to lower the B. M. R. further, as shown in Figure 2. This patient, ready for operation after 17 days of treatment, could not be operated upon because of oral sepsis. A further 23 days of treatment only served to lower the rate further, finally producing clinical myxedema, at which point the patient was operated upon.

OPERATIVE AND POSTOPERATIVE CHARACTERISTICS OF THE THIOURACIL-TREATED PATIENT

As has been pointed out previously, some of the glands show an unusual degree of hyperplasia histologically and a grossly increased vascularity after thiouracil preparation. In an occasional patient the vascularity may be sufficiently exaggerated to hamper the surgeon and complicate the operation. This phenomenon was of surgical significance in three of the 34 operated cases.

The operative course of this group of patients was satisfactory from the standpoint of pulse and blood pressure responses. Indeed, in many instances the even pulse and blood pressure readings over a two-hour period were quite striking and most unexpected for the degree of thyrotoxicosis existing previous to treatment. The intra-operative blood pressure and pulse response has been used[9] by the resident surgeons of this hospital for some time as one of the chief criteria in selecting hemithyroidectomies as the surgical treatment for any given case. In this group of thiouracil-treated patients none required hemithyroidectomies for this reason. One patient prepared for her first operation with iodine (B. K. No. 24323)

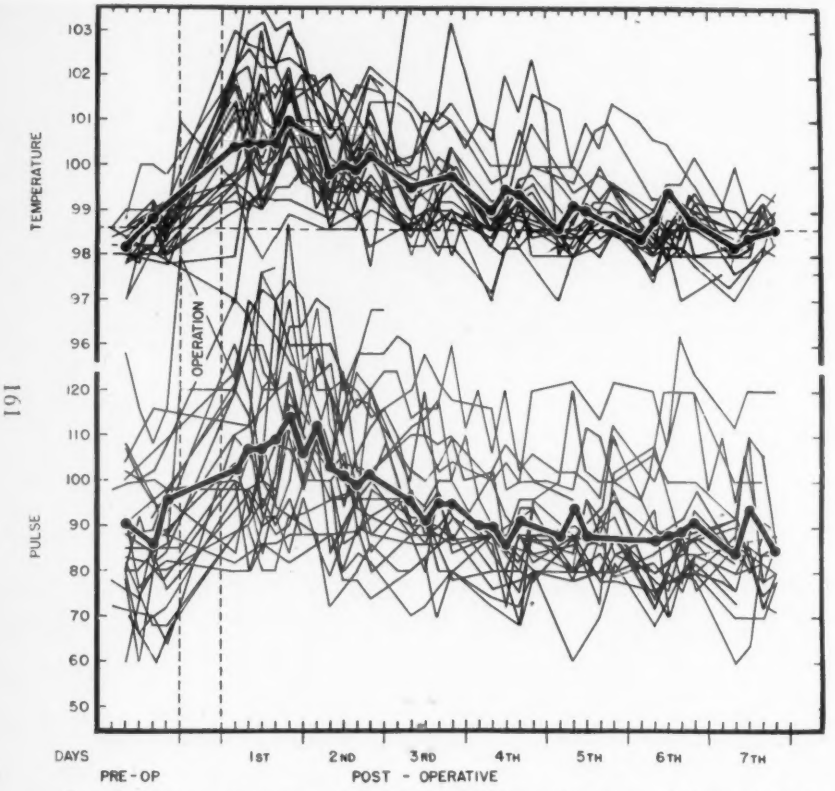


FIG. 6.—Postoperative temperature and pulse readings of a group of thyrotoxic patients prepared for operation with iodine. The heavy line is the average; there is a wide spread in the readings with many temperatures over 102° F., and many pulse rates over 120.

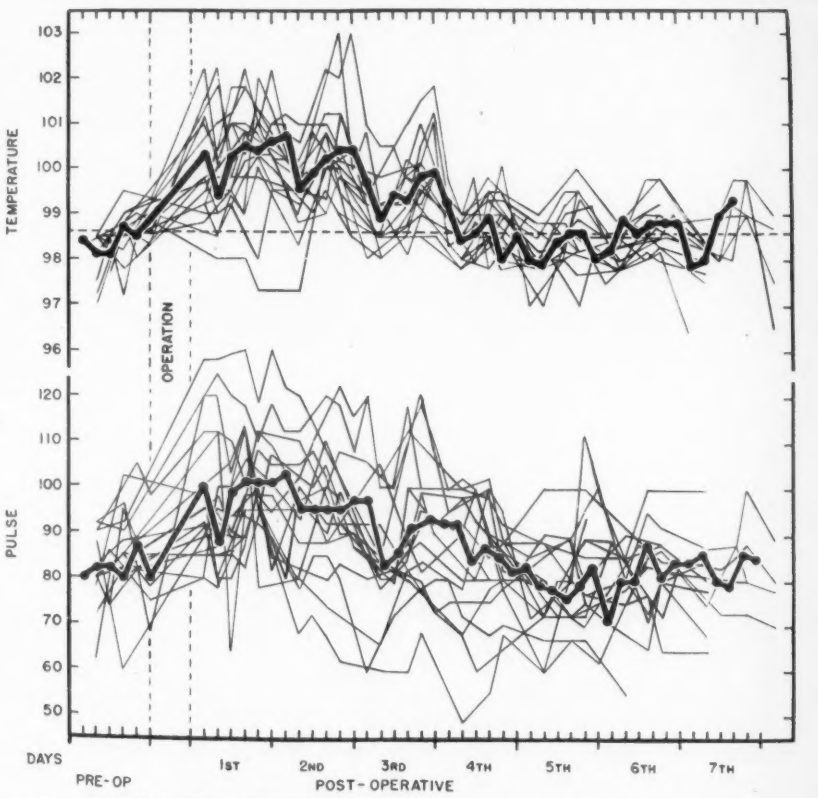


FIG. 7.—Postoperative temperature and pulse readings of a group of thyrotoxic patients prepared for operation with thiouracil. The heavy line is the average, and is not significantly lower than the iodine curves (Fig. 6); however, there is much less variation in the readings, with only two temperatures over 102° F., and only one pulse rate consistently over 120.

necessitated hemithyroidectomies and was prepared for her second operation with thiouracil. Another patient (M. S. No. 23309) was selected for hemithyroidectomies preoperatively because of the presence of a large iodine-fast goiter and the development of a leukopenia while on thiouracil. Actually, her operative response during the first operation was entirely uneventful.

Charts showing the postoperative response of the thiouracil group as compared with the control group of cases are shown in Figures 6 and 7. In Figure 6 is shown the postoperative temperature and pulse readings for a group of iodine-treated thyrotoxic patients. There is a wide spread in the readings, with many temperature readings over 102° F., and many pulse rates over 120, some up to 160. The average, shown by the heavy line, is not excessive in either respect. The thiouracil-treated postoperative cases are shown in Figure 7. Here, the average temperature curve is not significantly lower than in the iodine cases. The pulse average is lower, however, barely going over 100 where the iodine-treated group shows an average over 100 for a 24-hour period. In the case of both temperature and pulse readings the spread is much less in the thiouracil cases. Only two temperatures rise over 102° F., and these both in the second day, due to minor degrees of atelectasis, not on the basis of thyrotoxicosis. Only one pulse stays over 120 for several readings.

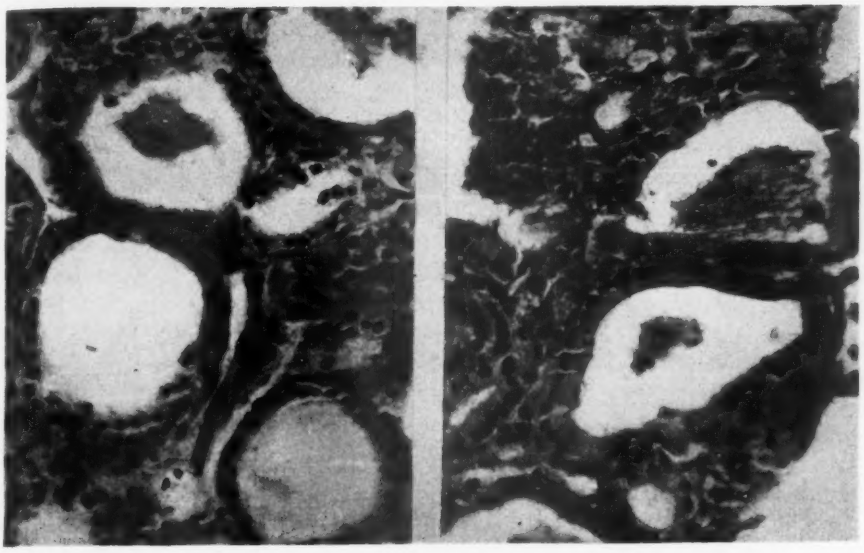
The postoperative course of the thiouracil-treated patients has been smoother than that we have become accustomed to expect following the preoperative preparation with iodine. The course has been more disturbed than in patients following resection of a nontoxic goiter, however, as evidenced by frequent temperature readings between 100° F and 101° F. on the first and second postoperative days.*

It is apparent, therefore, that though the metabolic rate is reduced to normal by the thiouracil, the entire physiologic status of the patient is not in equilibrium; the autonomic nervous system is still to some degree disturbed. This is a manifestation of the fact that though thiouracil inhibits the formation of thyroid hormone, it does not affect the underlying etiologic mechanisms of thyrotoxicosis; this fundamental autonomic imbalance persists, and may be responsible for the residual postoperative thermal responses seen in many of our cases.

HISTOLOGIC AND METABOLIC OBSERVATIONS

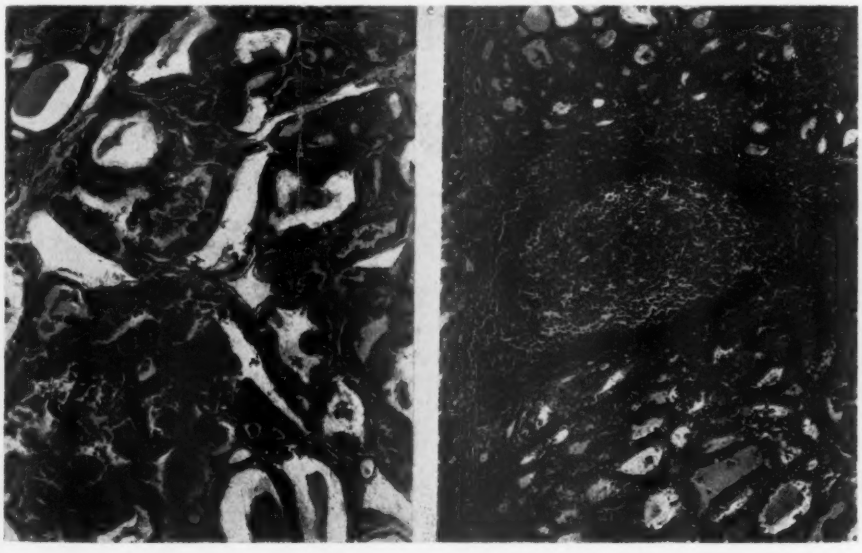
The surgically-removed thyroid glands when examined histologically showed, in contrast to the involution observed in iodinized thyroids, hypertrophy or marked hyperplasia, with diminished or absent colloid. In view of this hyperplasia and in view of the marked hyperplasia observed in the experimental goiters produced in animals by the administration of thiouracil, a very natural question presents itself: "Does the administration of thiouracil

* One patient developed paroxysmal auricular fibrillation postoperatively. She had a large retrosternal gland, and manipulation in the anterior mediastinum was necessary in order to remove it. The fibrillation was controlled by quinidine and digitalis, and might have been prevented by the preoperative use of these agents.



A B

FIG. 8.—Sections of thyroid from patient F. D. (No. 24336) taken (A) before initiating thiouracil treatment, and (B) after 20 days of treatment. The acinar cell height has been increased an average of 4.2 micra.



A B

FIG. 9.—Section of thyroid from patient B. B. (No. 422660) taken (A) before starting thiouracil treatment, and (B) after 17 days of therapy. The normal structure of the thyroid has been partially replaced by lymphoid tissue and the remainder shows extreme hyperplasia.

in hyperthyroidism increase the already existent thyroid hypertrophy and hyperplasia?" With this question in mind, biopsies were done on the thyroids of five patients before thiouracil therapy was started. The histologic picture of the biopsy specimen was compared with the histologic appearance of at least four different areas from the glands removed at operation.

These preparations were examined under oil immersion and the height of one representative cell from each of 100 successive acini was determined in each slide. Some increase in the mean acinar cell height was observed in the thyroids of all patients studied, indicating increased hyperplasia in the thiouracil-treated glands. In one patient the increase in mean cell height averaged 4.2 micra (Fig. 8). In another patient the biopsy showed only hypertrophy and hyperplasia; several specimens of the surgically removed thyroid examined after treatment with thiouracil showed, in addition to the hypertrophy and hyperplasia of the acinar cells, hyperplasia of lymphoid tissue. In several areas (Fig. 9) the acinar structure of the thyroid was almost completely replaced by lymph follicles.

The most prompt clinical and B. M. R. responses were observed in those patients whose thyroids, on histologic examination, showed marked hyperplasia and practically no stored colloid. As an example, a 20-year-old girl (E. K. No. 24085), who had classic exophthalmic goiter of moderate severity, showed a basal metabolic rate before starting treatment of +38. Clinical improvement was rapid on thiouracil, and by the tenth day of therapy the metabolic rate had fallen to +2. The histologic picture of the resected thyroid, shown in Figure 10, was that of marked hyperplasia with almost complete loss of colloid.

A further example of this phenomenon is shown by another 20-year-old girl (F. P. No. 24282) who on admission to the ward appeared extremely toxic. With bed rest and sedation she improved. Her B. M. R. level before starting treatment with thiouracil was +35. She made a good response to thiouracil and in 17 days her metabolic rate had fallen to +7. The evening before scheduled operation she developed a fever which was due to two dental abscesses. Thiouracil administration was continued, the dental abscesses were drained, and the infected teeth removed. Within 30 days the metabolic rate had fallen to —16 and the patient appeared to be myxedematous. Operation was performed on the 40th day of thiouracil treatment. Her thyroid was found to be so hyperplastic that in some parts of the gland the acinar structure was completely replaced by columns of epithelial cells, as shown in Figure 11. In this patient, after 40 days of therapy, clinical myxedema coexisted with extreme histologic hyperplasia.

In contrast, is the example of an 18-year-old male (W. L. No. 24260) admitted to the hospital wards with moderately severe thyrotoxicosis, and a B. M. R. level of +40. He made a slow response to treatment with thiouracil. The B. M. R. fell to +12 in 30 days. The thyroid (Fig. 12), even after treatment, was found to be involuted with practically no hyper-

FIG. 10

FIG. 11

FIG. 10.—Sections of thyroid removed from patient E. K. (No. 24038) after ten days of thiouracil treatment. There is virtually complete loss of colloid in an extremely hyperplastic gland.

FIG. 11.—Histologic section of thyroid gland from patient F. P. (No. 24282) after 40 days of thiouracil treatment. Although the histologic appearance is that of extreme hyperplasia, the B.M.R. was −16, and the patient clinically myxedematous.

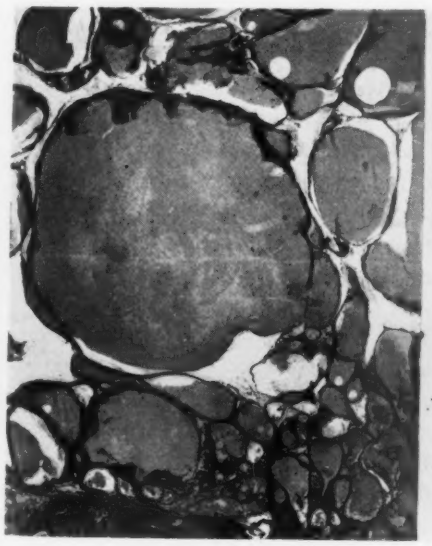


FIG. 12

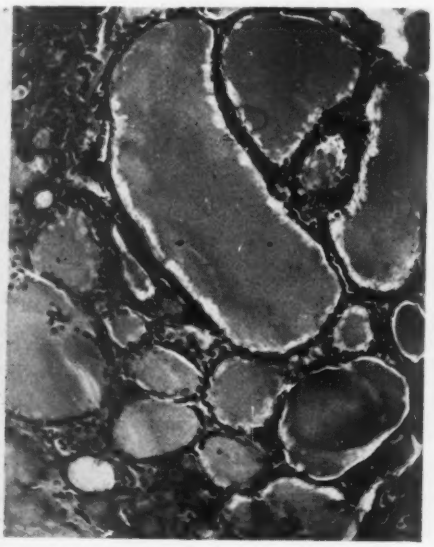


FIG. 13

FIG. 12.—In contrast to the previous photomicrographs, this section from the thyroid of patient W. L. (No. 24260) shows the appearance of an iodinized thyroid following 30 days of treatment with thiouracil. It is evident that involution still predominates with only slight superimposed hyperplasia.

FIG. 13.—Microscopic appearance of a long-standing colloid goiter, recently become toxic, after 22 days of thiouracil treatment. (Pt. M. B., No. 24273). As in the iodinized gland, involution predominates.

plasia, a fact difficult to reconcile with our other experiences with untreated cases. After the thyroid sections had been examined the patient was again asked about previous therapy, and he then admitted having taken iodine for several weeks before admission to the hospital. This disclosure of previous iodinization explained the apparently incongruous findings.

Also in contrast, a 49-year-old housewife (M. B. No. 24273) entered the hospital for treatment of palpitation. She had had a large goiter for 15 years, and had had mild symptoms of thyrotoxicosis for five months. She had a B. M. R. level of +20. After 22 days of treatment with thiouracil the basal metabolic rate fell to +7. The operatively removed thyroid examined histologically revealed involution with little hyperplasia, as shown in Figure 13.

Astwood[5] has advanced the theory that thiouracil acts by preventing the completion of physiologically active hormone and that it does not affect the preformed hormone. Our observations that the most rapid clinical and B. M. R. responses to thiouracil treatment were observed in those patients whose thyroids originally showed hyperplasia and practically no colloid, support Astwood's theory.

In ten of the patients who had been prepared for thyroidectomy with thiouracil the uptake of radioactive iodine (eight-day half-life) was studied. Each of these patients was given a tracer dose of radioactive iodine (150 micrograms of iodine as sodium iodide) 24 to 48 hours before operation. All of the urine excreted from the time of radioactive iodine administration to the time of operation was collected in 24-hour amounts. The per cent of radioactivity excreted in the urine then was determined, as well as the amount of radioactive iodine contained in the thyroid at the time of operation. In general, it was observed that most of the administered iodine was excreted in the urine and that very little radioactivity was demonstrable in the thyroid tissue.[11] This is in distinct contrast to the reported[12] findings in untreated thyrotoxicosis and lends considerable support to Astwood's theory; it suggests further that the "block" in elaboration of hormone takes place at the level of iodinization.

TOXICITY

Thiouracil appears to exhibit a degree of toxicity similar to the less toxic sulfonamides whose toxic properties it resembles. Amongst 52 patients treated to date we have observed two leukopenias, four oral infections possibly related to the drug, and a generalized lympadenopathy which cleared after stopping the drug at operation. Dr. Astwood* has observed a leukopenia while treating a patient with 2.0 Gm. per day, and four drug fevers. Drug fever and rash have been reported in the literature; in two of our patients the development of a fever was associated with sensitivity to the drug as manifested by an abrupt rise in temperature to 103° F. after a single dose of thiouracil, following a few days' cessation of dosage.

* Personal communication from Dr. E. B. Astwood.

The leukopenias observed in two of our patients involved a fall in white count to the neighborhood of 2500; the percentage of polymorphonuclear leukocytes never fell below 30 per cent. In one patient the drug was continued with return of the count to normal. In another, the drug was stopped. The dental infections and gingivitis observed in two patients involved postponing operation but did not alter the outcome of treatment.

In no case has any toxic manifestation either complicated operation or involved abandonment of surgery. In the two patients who developed drug sensitivity, with fever, preoperative preparation was completed with iodine. Because these two patients did not come to operation on thiouracil, they are not included in Table 1.

COMMENT

Thiouracil changes profoundly the function of the thyroid gland. The experimental observations and the initial clinical observations of Astwood with this drug have been amply confirmed. The place of the drug in the treatment of hyperthyroidism, however, has not been settled finally.

At the Massachusetts General Hospital we have reserved the drug in nearly all instances for the preparation of patients for thyroidectomy. As such it is more effective than iodine or any other previously tried agent or combination of methods. If used correctly, the metabolic rate of the patient is reduced to normal or lower. From the point of view of metabolic rate the operative risk, therefore, is apparently that of the patient with nontoxic goiter. Both the operative and postoperative courses of the patient who has been prepared with this drug are less tempestuous than the patient prepared with iodine, in whom there is usually a residual elevation of metabolic rate. It should be pointed out, however, that in a few patients, even though the basal metabolic level was well within normal limits immediately before operation, there were upheavals of cardiac function and rises of body temperature after operation reminiscent of the patient operated upon with active hyperthyroidism. Although clinical improvement paralleled the drop in metabolic rate, the entire physiologic state had not returned to normal. This may indicate that thyrotoxicosis is essentially a biphasic disorder—one phase the result of cellular metabolic changes produced by thyroid hormone in excessive amounts; and the other phase a more fundamental etiologic process related either to the pituitary or autonomic nervous system, or both. Thiouracil can alter only the metabolic phase of the disease (by blocking the iodinization of the hormone), leaving the underlying autonomic or endocrine disorder unchanged. It is this latter aspect of hyperthyroidism which must be approached in future therapeutic endeavors, and which at present produces some postoperative upheaval in the patient prepared with thiouracil.

Since the usefulness of the drug as far as operation is concerned lies in the reduction of the metabolic rate to normal, it is unfortunate that those patients needing the drug the most, the thyrocardiacs, are the ones in whom

the drug takes the longest to act. The thyrocardiac represents the patient carrying the worst surgical risk. These are usually patients in the older age-group, in whom the limited cardiac reserve of age has been completely absorbed by the excessive cardiac load of thyrotoxicosis and in whom, therefore, the added burden of operation is prone to initiate serious decompensation. Such patients have often had long-standing, well involuted goiters. The colloid presumably stored in these glands delays the clinical effectiveness of thiouracil. Several weeks or a month of therapy, with the patient bedridden, may be needed before improvement is adequate for operation. The advantages of the drug, however, outweigh the disadvantages of prolonged preparation, unless the patient's toxicity is very mild. In any case selected for treatment the drug should be started and no considerations short of frank toxicity should dissuade the clinician from continuing it until the full benefit is obtained and the B. M. R. is at 0 or below.

Knowing that Doctor Astwood and others were centering their attention on the possible medical cure of hyperthyroidism with thiouracil, this clinic has treated but few cases with thiouracil and without surgery. It is perhaps unwise to compare at this stage his observations with ours, but certain pathologic and physiologic considerations in regard to the eventual medical therapy of hyperthyroidism with this drug are of importance at present. Thiouracil is goitrogenic; given to one patient in the absence of hyperthyroidism it produced an acute hyperplastic goiter similar to that encountered in a patient following thiocyanate therapy. Thiouracil also increases hyperplasia in the patient suffering from hyperthyroidism. From an anatomic point of view, therefore, it enhances the primary anatomic change of the disease. Iodine, in contrast, reverses the disease anatomically by inducing involution. An anatomic reversal similar to that of iodine would seem more likely to produce permanent relief as a means of medical treatment.

Ideally, having blocked the formation of thyroid hormone with thiouracil, it would be advantageous to produce regression of the resultant anatomical changes by the use of thyroid or iodine, as a preliminary to operation. This has not been done in enough cases, as yet, to permit a report as to its usefulness.

In recurrent thyrotoxicosis one must bear in mind that the increased vascularity of the gland may be especially troublesome, working in a scarred field. In any case, the surgeon must use care and caution in his operation as the hyperplasia and vascularity of the gland may render a hurriedly done procedure unnecessarily bloody.

SUMMARY AND CONCLUSIONS

1. Thiouracil has been administered to 53 thyrotoxic patients as a preparation for thyroidectomy. Of these, 34 have come to operation and been followed long enough to form the basis of this study. Of these 34, 26 have received thiouracil as the only preparative drug.

2. Thiouracil is superior to iodine as a preparation for thyroidectomy

because, regardless of the degree of elevation of the metabolic rate prior to therapy, it will bring the patient to operation with a normal metabolic rate.

3. The histologic change accompanying this lowering of the basal metabolic rate is an intensification of the hyperplasia seen in thyrotoxicosis. Thiouracil produces an hyperplastic but nonfunctioning goiter.

4. An occasional disadvantage of the use of thiouracil in preparing patients for surgery lies in the fact that this hyperplasia is accompanied by an increased vascularity and friability which makes the gland more difficult to handle and renders hemostasis arduous.

5. The increased vascularity is especially troublesome if the patient has had a previous thyroidectomy.

6. Preliminary, or concomitant, iodine administration delays the thiouracil response; it is possible but not yet proven that iodine therapy subsequent to thiouracil treatment may play a useful rôle in reducing hyperplasia and vascularity.

7. Toxicity not unlike that of the sulfonamides may be expected to occur when treating patients with thiouracil.

8. Thiouracil, while an improvement over iodine as a means of preparing patients for surgery, is not yet the ideal drug for this purpose because it increases the histologic abnormality of the disease; because it affects only the production of hormone and not the underlying etiology of hyperthyroidism; because surgery may be rendered more difficult by it, and because disturbing evidences of toxicity may become manifest.

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SUBTOTAL GASTRECTOMY FOR DUODENAL ULCER*

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IT IS INEVITABLE in the treatment of any disease that certain progressive changes are bound to occur with the accumulation of experience. On July 1, 1937, a new group of surgeons was delegated to care for ward patients suffering from peptic ulcer. In the course of the ensuing six years, certain modifications were gradually evolved in preoperative management, anesthesia, operative technic and postoperative care. The ultimate aim of these innovations was the diminution of the morbidity and mortality incident to the surgical therapy of duodenal ulcer. In an effort to determine the efficacy or failure of these changes, a detailed study was made of the records of all ward patients upon whom a subtotal gastrectomy was performed for duodenal ulcer. It was possible for comparative purposes to divide these cases into two series: Series A: 79 patients (July 1, 1937 to June 30, 1940); and Series B: 94 patients (July 1, 1940 to June 30, 1943).

It is granted that duodenal ulcer, in its incipiency, is not a surgical problem. It only becomes one when certain complications occur which do not respond to medical therapy. These are, excluding acute perforation, the failure of repeated medical "cures" to relieve persistent pain, severe and recurrent hemorrhages, and intractable pyloric or duodenal stenosis. All patients in this series presented one or more of these complications, but no patient was operated upon without the approval of an internist or gastro-enterologist.

HISTORY

The ulcer symptoms had been present in the majority of patients for many years. This is readily appreciated in reviewing Table I.

TABLE I

	DURATION OF DISEASE				
Approximate years duration	3 years	5 years	10 years	15 years	20 years
Number of cases	53	51	34	21	14

The chronicity of the disease may be seen by a brief statistical study of the symptomatology listed in Table II.

This series of 173 cases was further divided, mainly on a basis of the history, into the following three groups:

* Read before The Surgical Section, New York Academy of Medicine, May 5, 1944.

TABLE II

SUMMARY OF IMPORTANT FACTS IN HISTORY

Intractable pain	156
One or more episodes of hemorrhage	73
Evidence of obstruction as shown by repeated vomiting, morning gastric retention of more than 500 cc., or 50% residue of barium in six hours	50
Patients with previous hospital admission for medical therapy of ulcer	78
Patients with previous hospital admission for perforation of ulcer	26

Group A: Patients with intractable pain, unrelieved by repeated medical treatment, many of whom had one or more hospital admissions for an ulcer "cure." The majority had had episodes of gastro-intestinal bleeding, and not a few were suffering from the effects of pyloric or duodenal obstruction.

Group B: Patients with actively bleeding ulcers. This group was composed of those who entered the hospital during or within a week of severe gastro-intestinal hemorrhage, and in whom the hemoglobin was below 60 per cent (Sahli). Only one patient was operated upon during the acute phase of a massive hemorrhage; the remainder were explored when the bleeding had apparently ceased. This group did not include patients who described several episodes of bleeding, but who entered the hospital in the interim, nor those who subsequently were readmitted for surgery after convalescence from a previous exsanguinating hemorrhage. These cases, when operated upon, were placed in Group A.

Group C: This group comprised those patients in whom an acute perforated duodenal ulcer had previously been sutured, and in whom a recurrence of active ulcer disease or mechanical obstruction had developed.

The relation of sex and age in these three groups is given in Table III.

TABLE III

ANALYSIS OF AGE AND SEX IN SUBGROUPS

	Sex		Ages					
	Male	Female	10–19	20–29	30–39	40–49	50–59	60 plus
A. Duodenal ulcer: 115 cases	94	21	0	12	27	42	34	0
B. Bleeding duodenal ulcer: 32 cases	31	1	0	6	7	13	3	3
C. Previously perforated duodenal ulcer: 26 cases	25	1	1	3	8	8	5	1
Total 173 cases	150	23	1	21	42	63	42	4

PHYSICAL EXAMINATION AND LABORATORY DATA

A general physical examination was made by a member of the surgical staff, and an internist especially assigned to the ward surgical service for this purpose. The physical findings were variable. Evidences of recent weight loss and dehydration were found in those who had suffered the effects of intractable pain and pyloric obstruction. A slight anemia was present in most patients. Some patients in whom the bleeding had been severe were quite pale, showing definite clinical evidence of recent pronounced blood loss; however, it was rather interesting that in ten cases the hemoglobin was over 100 per cent. The association of polycythemia and duodenal ulcer has frequently been mentioned.

Chemical examination of the blood was routinely made for evidences of azotemia, hypoproteinemia and alkalosis. In two cases only, in which vomiting had been severe and protracted, were the clinical signs of alkalosis, as evidenced by tetany, readily discernible. However, the blood examinations revealed definite chemical evidences of alkalosis in seven other patients. This small number probably does not represent a true index of the frequency of this complication, for in this series adequate parenteral therapy was instituted frequently before the blood was drawn for chemical determinations. Varying degrees of azotemia and hypoproteinemia were present in many patients.

An increase above normal in the free and total acidity was uniformly observed in the Rehfuss test meals and in the examinations of the night-fasting gastric contents. Gastric analysis after the administration of insulin was done on a few patients in whom vagotomy was anticipated as a complementary procedure to subtotal gastrectomy.

Fluoroscopic and roentgenologic examinations were performed before or during hospital admission. The characteristic finding was a deformity of the duodenal bulb and occasionally an ulcer crater. Appreciable gastric retention of barium was found in 51 cases, but this roentgenologic finding was not always confirmed by the clinical evidences of retention. Gastroscopic examinations in patients suffering from duodenal ulcer were found to be of no direct value.

PREOPERATIVE PREPARATION

The majority of these ward patients who had suffered for many years from the devitalizing effect of chronic recurrent ulceration were in exceedingly poor general condition. Many showed the effects of severe physicochemical imbalances, the results of inadequate nutrition, intractable pain, persistent vomiting, or bleeding. As a group, these patients were obviously poor operative risks, and, therefore, required careful preoperative preparation.

All patients were given a period of complete bedrest. Whenever possible, a high protein diet was prescribed, and essential vitamins were administered orally or parenterally. Pain was controlled with mild sedatives, aluminum hydroxide, atropine, frequent bland feedings and, occasionally, the milk or amphojel drip, as advocated by Winkelstein, Cornell and Hollander.[1, 2] Anemic patients were given repeated transfusions of whole blood until the hemoglobin was raised to above 80 per cent. Every patient received a daily intravenous infusion of 1500 cc. of saline and glucose. This was increased to about 4000 cc. if vomiting had been a prominent symptom and a negative oral fluid balance existed because of pyloric obstruction. In these cases, the dilated atonic stomach with its stagnant contents was lavaged morning and evening with hot water through a large gastric tube. The importance of these lavages cannot be overemphasized. As a rule the inflammatory reaction about the duodenum or spasm of the pylorus subsided sufficiently so that gastrointestinal continuity was restored with the cessation of vomiting, a marked diminution in pain, and a general clinical improvement of the patient.

Hypoproteinemia, which was not infrequent, usually responded to a high protein diet. If this was not feasible, plasma and blood transfusions, often supplemented by the intravenous use of amino-acids, elevated the lowered blood proteins to approximately normal levels. A preliminary jejunostomy for alimentation was performed in two patients suffering from pyloric obstruction, hypoproteinemia and alkalosis, who had failed to improve under conservative medical management. Their response to jejunal alimentation was immediate and striking, for within a short time gastroduodenal continuity was restored and the chemical imbalances were corrected. Subsequent subtotal gastrectomy was followed by uneventful recovery.

Twenty cases were treated preoperatively with therapeutic doses of desoxycorticosterone, but as no definite benefits were noted empirically, its use was discontinued. Sulfonamides were not used preoperatively.

ANESTHESIA

Inhalation anesthesias of various types were administered during the first three years. During the second three years, continuous spinal anesthesia was used, with ever increasing frequency. The total dosage injected was about 200 mg. of procaine hydrochloride. Patients who were unduly apprehensive, or otherwise uncooperative, were given small doses of pentothal sodium intravenously. Continuous spinal anesthesia provided such excellent relaxation that adequate exposure was obtained with relatively few intra-abdominal packings and little retraction. Unfortunately, however, it did not diminish the incidence of pulmonary complications, which still contribute, in large part, to the morbidity and mortality of the operation.

OPERATIVE PROCEDURE

The incision regularly employed was midepigastric, extending from the ensiform cartilage to the umbilicus. This was found to give adequate exposure in most cases. In a few especially obese patients, a right subcostal incision from the ensiform to the tip of the eleventh rib provided better access to the duodenum.

The operation of choice for duodenal ulcer in this clinic is still subtotal gastrectomy of the Billroth II-type. It is felt that this operation affords relief of symptoms in most cases, and is followed by the minimal incidence of recurrent gastrojejunal ulceration. But this operation is a complicated technical procedure, which is often extremely difficult even in the hands of the more experienced. It is certainly not applicable to all patients suffering from chronic recurrent duodenal ulceration. It was contraindicated usually in those whose general poor condition did not respond to preoperative supportive treatment, in those who were extremely obese, in those who had passed the age of 65, and in those afflicted with severe cardiac disease or chronic nephritis. In these cases, a gastro-enterostomy was performed. In the six-year period, in which 223 patients were explored for chronic recurrent duodenal ulcer, a gastro-enterostomy was performed upon 48 patients, a pyloroplasty upon two patients, and a subtotal gastrectomy upon 173 patients.

TABLE IV

CHOICE OF OPERATIONS

	Number	Per Cent
Total chronic duodenal ulcers operated upon	223	
Subtotal gastrectomy	173	77.6
Posterior gastro-enterostomy	48	21.5
Pyloroplasty	2	0.9

Initially, the method of gastric resection, developed by Berg[3] and Lewisohn,[4] was followed. Gradually, however, definitive departures in technic were made. These will be only briefly described. After ligating the four cardinal arteries at appropriate points the stomach was transected proximal to the reentrant angle between a double layer of clips, laid down with the DePetz sewing machine. The distal gastric segment was turned to the right and the duodenum was carefully mobilized and divided by the open method, removing the ulcer whenever possible and practical. This frequently presented difficulties when the ulcer was extensive and the surrounding tissues were edematous, brawny and friable, or when the lesion penetrated deeply into the pancreas, or occupied the second portion of the duodenum.

TABLE V

PATHOLOGY

Location	Number
Anterior wall (superior)	105
Posterior wall	48
Kissing type (anterior and posterior walls)	15
Second portion of duodenum	5

We do not feel that excision of the ulcer is an essential part of this procedure provided the pylorus is removd. (This was not undertaken in three cases in which a prepyloric "*auschultung*" was performed). In the present series of 173 cases, 102 resected specimens were found to contain the ulcer when examined by the pathologist. With the complete side-tracking of the acid gastric contents, any ulcer in the isolated duodenum, bathed in its alkaline secretions, will heal completely. Recurrence of an ulcer in the duodenal stump is practically unknown. Furthermore, Mage,[5] in a carefully conducted follow-up study of patients who had had a previous subtotal gastrectomy, concluded that recurrent gastrojejunal ulceration was no more frequent in those patients in whom duodenal ulcer was left *in situ* than in those in whom it was excised.

The great hazard of subtotal gastrectomy centers about the successful closure of the transected duodenum. The initial chromic Connell inversion suture was reinforced with interrupted linen Lembert sutures. An attempt was made to bring the stump of the divided pyloric artery over the superior angle of the sutured duodenum, and the stump of the divided gastro-epiploic artery over the inferior angle. The closed duodenum was then buried against the head of the pancreas with interrupted plain catgut sutures.

Drainage of the duodenal stump has been used with greater frequency during the past three years because of the possibility of a duodenal dehiscence.

It has become routine in almost all cases in which the security of the duodenal closure was questioned. A rubber dam, introduced through a right subcostal stab incision, was sutured with plain catgut to the duodenal stump. For a time, ten grams of sulfanilamide were deposited in this area, but this procedure has been abandoned.

Following resection, gastro-intestinal continuity was established at first by the usual retrocolic terminolateral gastrojejunostomy of the Hoffmeister-type. During the past three years this isoperistaltic anastomosis has been made *anterior* to the colon, utilizing a short proximal loop of jejunum, about six inches long. In an extensive and careful follow-up, no differences have been noted in the functioning of the anterior anastomosis as compared with the posterior anastomosis. We have been impressed with the simplicity and advantages of the antecolic gastrojejunostomy. It has made the operation somewhat easier and has eliminated the incision in the transverse mesocolon which caused difficulty in six patients in whom the mesocolon was short. If subsequent gastrojejunal ulceration should develop at the site of this anterior anastomosis (which has not yet occurred in this series) secondary resection of the jejunum and stomach would certainly be less complicated. There is less possibility of the anastomotic ulcer penetrating into the colon and no possibility of injury to the middle colic artery in secondary operative procedures.

If, at the time of exploration, the stomach was markedly atonic and dilated, or if an appreciable retention has been present prior to operation, or if the duodenal closure was difficult and dehiscence of the suture line was a possibility, a complementary jejunostomy of the Kader-Stam type was performed for alimentation. This permitted feeding of a special pabulum containing all essential foods, vitamins, and electrolytes within 24 hours after operation, and resulted in the early curtailment of parenteral feeding. If a duodenal fistula developed, the drainage, if profuse, was immediately aspirated by continuous suction, using the Stedman pump, thereby protecting the skin from the ravages of pancreatic digestion. The aspirated material containing intestinal, pancreatic, and biliary secretions was subsequently introduced through the jejunostomy tube. In some cases of gastric atony in which the drainage from the indwelling Levin tube was excessive and prolonged, the instillation of the acid gastric secretion into the jejunostomy aided in the prevention of alkalosis. A complete discussion on the advan-

TABLE VI

	Stgr.*	Stga.†	Jejunostomy			Drainage	
			Comp.	Prel.	Sup.‡	Yes	No
A. Duodenal ulcer	27	88	24	1	0	66	49
B. Bleeding duodenal ulcer	11	21	2	1	1	19	13
C. Previously perforated duodenal ulcer	9	17	6	0	1	16	10
	47	126	32	2	2	101	72

* Subtotal gastrectomy with retrocolic terminolateral gastrojejunostomy.
† Subtotal gastrectomy with antecolic terminolateral gastrojejunostomy.
‡ Complementary, preliminary, supplementary.

tages of jejunostomy for alimentation has been described elsewhere.[6] Table VI lists the type of gastro-enteric anastomosis, the institution of drainage, and the use of jejunostomy in each of the three groups.

After the operation has been completed, the median epigastric incision was closed with heavy silk sutures passed through all the layers of the abdominal wall. This type of closure can be effected rapidly, and wound dehiscence, with evisceration, which was formerly frequent in midline incisions, has been practically eliminated. This type of closure, however, is accompanied by an appreciable number of postoperative herniae.

POSTOPERATIVE COURSE AND COMPLICATIONS

Postoperatively, a Levin tube was left indwelling and an intravenous infusion of saline and glucose, which was given throughout the operation, was continued. If there was moderate blood loss or any degree of shock, the patient was transfused. Oral fluids in small amounts were allowed within 24 hours after operation. Sulfonamides were not administered routinely.

The Levin tube was usually removed about the third day, unless signs of gastric retention were evident. Adequate sedation was administered. The patients were encouraged to move about. The through-and-through sutures were removed in ten days, at which time patients were permitted out of bed.

There were no instances of immediate postoperative hemorrhage. Two patients experienced a small hematemesis about the tenth day, but this was easily controlled with conservative measures.

Difficulties in gastric emptying were not unusual, but in the majority of patients these were transitory and without significance. A severe gastric atony occurred in three cases in which a complementary jejunostomy had not been undertaken. In one patient, an entero-anastomosis was performed 14 days after the primary operation, without relief of the gastric ileus. Subsequent postmortem examination failed to disclose any mechanical reason for the vomiting and alkalosis. This case impressed us with the seriousness of this complication, and was the reason for the subsequent frequent institution of complementary and supplementary jejunostomy for alimentation in indicated cases. In two other patients suffering from gastric atony, a supplementary jejunostomy, because of an alkalosis, was performed within a week of the primary operation, and recovery was uneventful.

Physical signs of a localized peritonitis were occasionally present in the right upper quadrant of the abdomen, and in some, a mass eventually became palpable. This was due probably to an inflammatory exudate about the duodenum and pancreatic head. In the majority of cases this subsided spontaneously, but in two patients an incision and drainage of an abscess became necessary. However, if the entire abdomen was tender and rigid, a general peritonitis arising from duodenal dehiscence was suspected. A duodenal leak was usually a fatal complication if the duodenal stump had not been drained. It almost inevitably resulted in a generalized peritonitis, a subhepatic abscess, or a right or left subphrenic abscess. The small subhepatic collections were usually absorbed spontaneously, but once a

diagnosis of a subphrenic purulent accumulation was substantiated roentgenologically and by exploratory puncture, surgical drainage was performed. Subphrenic abscess was a serious complication and death occurred in three of five patients who were drained.

The danger from a duodenal leakage was materially lessened by the use of drainage which, as has been previously indicated, is being instituted with increased frequency. The presence of a rubber dam in the vicinity of the duodenal suture line apparently did little harm. There was evidence of duodenal drainage along the dam in approximately 13 cases, but in only two of these did a general peritonitis develop. Most duodenal leaks made their external appearance on the third or fourth day; others were not apparent until the ninth or tenth day. This varied in degree from a slight biliary staining of the dressing to a profuse intestinal discharge which was only controlled by continuous suction drainage with a Stedman pump. There were three cases in which, after the duodenal secretion had ceased, a purulent drainage persisted for three months. This was undoubtdly due to a residual infection about the linen Lembert sutures. All these sinuses, however, subsequently healed. There was no instance in which either a spreading peritonitis or localized intra-abdominal abscess could be ascribed to a dehiscence of any part of the Hofmeister type of terminolateral gastrojejunostomy.

Five patients became jaundiced postoperatively. The icterus in four cases was apparently the result of sulfonamide therapy. The fifth case was never properly explained, but the jaundice eventually disappeared, and the patient ultimately recovered.

Wound infections were rather infrequent, rarely contributed to the morbidity, and never to the mortality of the operation. In three cases in which the wounds were not sutured with the usual "through-and-through" closure, a disruption occurred, but no evisceration occurred in any cases in which the routine closure was used.

The incidence of pulmonary complications, which were mainly pneumonic and atelectatic in nature, was high. In a few seriously ill patients, a rapidly performed bronchoscopy with suction removal of the mucous plug was responsible for a prompt and dramatic recovery. While the judicious use of sulfonamides did much to render pulmonary complications less severe, there were five deaths attributable to pneumonia. One patient died of a pulmonary embolus, and one of a cerebral thrombosis.

An analysis of the mortality in the three previously described groups is outlined in Tables VII A and B. A résumé of the causes of 12 deaths, determined in nine instances by postmortem examination, is detailed in Tables VIII A and VIII B. A comparison of the two series is given in Table IX.

DISCUSSION

A study of Tables VII, VIII, and IX shows that there was a significant difference in mortality between Series A (July 1, 1937 to June 30, 1940) and

TABLE VII A

ANALYSIS OF DEATHS IN SUBGROUPS

Series A

	No. of Cases	No. of Deaths	Cause of Death	Mortality Rate
Duodenal ulcer	48	3	(1) Cerebral thrombosis (2) Generalized peritonitis (3) Alkalosis	6.25%
Bleeding duodenal ulcer	16	3	(1) Duodenal dehiscence Generalized peritonitis (2) Hemorrhagic bronchopneumonia (3) Subphrenic and subhepatic abscesses	18.75%
Previously perforated duodenal ulcer	15	2	(1) Massive atelectasis (2) Pneumonia after drainage of subphrenic abscess	13.33%
Total	79	8		10.13%

TABLE VII B

ANALYSIS OF DEATHS IN SUBGROUPS

Series B

	No. of Cases	No. of Deaths	Cause of Death	Mortality Rate
Duodenal ulcer	67	3	(1) Hepatitis and pneumonia (2) Pulmonary embolism (3) Diffuse bronchopneumonia	4.48%
Bleeding duodenal ulcer	16	1	(1) Duodenal dehiscence Subhepatic abscess	6.25%
Previously perforated duodenal ulcer	11	0		0
Total	94	4		4.26%

Series B (July 1, 1940 to June 30, 1943). In Series A, death was the eventual result of a duodenal leak in four cases, while in Series B this complication occurred in only one instance. The improvement was undoubtedly due in part to the increased skill of the operators in effectively mobilizing the duodenum so that its closure was more secure. Then, too, the wider use of drainage probably acted as a safety vent in those cases in which a duodenal dehiscence developed. If these cases had not been drained, a fatal generalized peritonitis might have resulted. This contention is further illustrated in the analysis of the causes of death in those patients who had had a previously perforated duodenal ulcer (Group 3, Table VII). In these secondary cases, the duodenum was fibrosed, distorted, and surrounded by firm dense adhesions. Mobilization was difficult, and closure was even more difficult. The fact that no deaths occurred in this group in which drainage was liberally used might be a commendation for this innovation.

The use of jejunostomy for alimentation, both as a complementary and supplementary procedure, undoubtedly prevented and corrected many of the physical and chemical imbalances incident to postoperative gastric atony and alkalosis. In the past, these serious and untoward complications have often contributed materially to the morbidity and mortality of gastric and duodenal surgery.

Spinal anesthesia provided better relaxation, and this, combined with the antecolic type of gastrojejunostomy, simplified the technical aspects of the entire operative procedure. It is to be noted in Table IX that the lowered

TABLE VIII A

DECEASED CASES—SERIES A

No. and Initials	Age and Sex	Diagnosis	Anesthesia and Operation	Cause of Death (Postmortem Findings)
455130 I. M.	56 Female	Duodenal ulcer. Arteriosclerotic cardiovascular dis.	Gas — oxygen — ether. Subtotal gastrectomy, with antecolic anastomosis. Drained.	Cerebral thrombosis, with hemiplegia (8 days P.O.). No postmortem obtained.
437484 M. S.	51 Male	Duodenal ulcer.	Avertin—ethylene. Subtotal gastrectomy, with retrocolic anastomosis.	Generalized peritonitis (8 days P.O.). No postmortem obtained.
432792 S. S.	41 Female	Duodenal ulcer. Hypertensive cardiovascular disease.	Avertin—ethylene. Subtotal gastrectomy, with anterior anastomosis. Secondary entero-enterostomy 14th P.O. day.	No anatomic reason for death. Clinical impression alkalosis (32 days P.O.).
424871 J. K.	55 Male	Bleeding duodenal ulcer.	Avertin—ethylene. Subtotal gastrectomy, with retrocolic anastomosis. (Auschultung, prepyloric).	Dehiscence of duodenal stump. Generalized peritonitis (7 days P.O.).
419123 K. H.	38 Male	Duodenal ulcer (previously perforated).	Avertin—ether. Subtotal gastrectomy, with antecolic anastomosis. Vagotomy.	Massive atelectasis. Pneumonitis (2 days P.O.). No postmortem obtained.
433621 A. L.	46 Male	Bleeding duodenal ulcer.	Avertin—ethylene. Subtotal gastrectomy, with antecolic anastomosis.	Severe hemorrhagic bronchopneumonia (16 days P.O.).
438885 D. E.	48 Male	Bleeding duodenal ulcer.	Avertin — ethylene. Subtotal gastrectomy, with retrocolic anastomosis. Drained. Supplementary jejunostomy for alimentation.	Subhepatic and subphrenic abscesses. Fibrinous peritonitis (42 days P.O.).
457697 B. S.	39 Male	Duodenal ulcer (previously perforated).	Ethylene. Subtotal gastrectomy, with antecolic anastomosis. Drained. Secondary drainage of left subphrenic abscess.	Pneumonia (died 6 days after drainage of subphrenic abscess, and 24 days after gastrectomy).

TABLE VIII B

DECEASED CASES—SERIES B

No. and Initials	Age and Sex	Diagnosis	Anesthesia and Operation	Cause of Death (Postmortem Findings)
485833 L. K.	58 Male	Duodenal ulcer.	Continuous spinal. Subtotal gastrectomy, with antecolic anastomosis. Drained. Intraperitoneal sulfanilamide.	Hepatitis and pneumonia (17 days P.O.).
491002 I. D.	54 Male	Duodenal ulcer. Essential hypertension.	Continuous spinal. Subtotal gastrectomy, with antecolic anastomosis. Intraperitoneal sulfanilamide. Drained.	Pulmonary embolism. Bronchopneumonia. Pulmonary edema (1 day P.O.).
501861 J. M.	58 Male	Duodenal ulcer.	Continuous spinal. Subtotal gastrectomy, with antecolic anastomosis. Drained.	Diffuse bronchopneumonia (7 days P.O.).
460231 J. B.	42 Male	Bleeding duodenal ulcer.	Cyclopropane. Subtotal gastrectomy, with antecolic anastomosis. Drained.	Dihiscence of duodenal stump. Generalized peritonitis (healing). Subhepatic abscess. Died 34 days P.O.

TABLE IX

COMPARISON OF THE STATISTICS IN SERIES A AND B

	Series A July 1, 1937 to June 30, 1940	*Series B* July 1, 1940 to June 30, 1943
No. of cases	79	94
Mortality	8	4
Mortality percentage	10.13	4.26
Drainage of duodenal stump	29	72
Antecolic type of gastrojejunostomy	35	91
Retrocolic type of gastrojejunostomy	44	3
Jejunostomy	4	32
Spinal anesthesia	16	84
General anesthesia	63	10

mortality in the second group may be ascribed in part to spinal anesthesia, the wider use of drainage of the duodenum, the antecolic type of anastomosis, and the frequent employment of jejunostomy for alimentation.

When the mortalities of the three groups are considered individually (Table VII A and B), it is found to be highest in the bleeding ulcers. In Series A the mortality was 18.75 per cent. Sixteen patients were explored as soon as blood and plasma transfusions had elevated the hemoglobin, increased the number of red blood cells and raised the blood pressure. There were three deaths. Apparently the impoverished tissues of the body were slow to recover from the recent effects of anoxemia so that healing was impaired, a dehiscence of the stump was more likely and pulmonary complications were more frequent.

In Series B, an equal number of patients were operated upon with one death, a mortality rate of 6.25 per cent. These patients were not explored until three to four weeks had elapsed following hemorrhage, and they had partially recuperated from the general systemic effects of their blood loss. In the future, all patients suffering from bleeding duodenal ulcer will be discharged from the hospital if possible, for convalescent care and radical surgery will be performed only when their general condition has approximated normal. This conservative attitude in the treatment of bleeding ulcer may be criticized by those who advocate early operation, frequently within 48 hours in those patients over 45 years of age. However, we agree with the conclusions of Crohn and Lerner[7] that, by and large, better results will be obtained in acute hemorrhage if these patients are treated medically during the acute phase. Radical surgery may then be subsequently performed when bleeding has ceased and the patients have fully recovered from the general effects of exsanguinating hemorrhage.

The problem of pneumonia is still apparently unsolved. The use of sulfonamide drugs and judicious application of bronchoscopy have undoubtedly lowered mortality from this complication, but pneumonia still seems to be an unavoidable and, only too often, fatal complication of upper abdominal surgery.

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HEMOSTASIS WITH ABSORBABLE GAUZE*

(OXIDIZED CELLULOSE)

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A PRELIMINARY REPORT of our observations of tissue reactions to oxidized cellulose† appeared in the ANNALS OF SURGERY in July, 1943. This represented experimental work undertaken in 1941, and the results agreed with those of Ingraham and Bailey, reported in 1944, who checked the tissue reactions and compared them to those obtained with fibrin foam.

In the same issue of the ANNALS Dr. Tracy J. Putnam reported his clinical use of the material as a carrier for thrombin to secure hemostasis in neurosurgery. At that time further investigation was planned to determine the degree of oxidation, *i.e.*, percentage of carboxyl groups, yielding the most satisfactory product for clinical use, and a reliable method for sterilization of the material, which does not withstand the process in the autoclave. At the moment of writing, the gauze supplied for clinical investigation contains approximately 13.5–15.8 per cent COOH, and is submitted, doubly packaged, in glassine envelopes after formaldehyde sterilization, which has been checked aerobically and anaerobically, and which does not leave sufficient trace of formaldehyde to render the material irritating on this account. Cotton pledgets, similarly packaged, contain 10–12.5 per cent COOH.

When the relatively nonirritating nature of the cellulose had been established, and it had been shown that, in small amounts at least, it was absorbed in varying lengths of time from different tissues, there was an immediate demand for the release of the gauze for clinical use in cases of hemorrhage where hemostasis could not be secured by ligature or other methods, and where ordinary gauze packing, with all the well known difficulties of subsequent removal, had to be used as a last resort. There were many suggestions offered as to use of the material in traumatic surgery, naturally, with military necessity in mind, where packing of wounds with ordinary gauze, used for

* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University.

† The gauze and cotton were supplied by Eastman Kodak Research Laboratories, Rochester, N. Y. (U. S. Pat. No. 2,232,900), through Parke, Davis & Company, Detroit, Michigan.

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hemostasis, had so often resulted in sealing-up of deep contamination, with resulting serious wound infection.

Accordingly, a series of experiments were undertaken to reproduce, as nearly as possible, lacerated bleeding wounds such as those which in clinical practice might necessitate gauze packing. No adjuvant to promote clotting was used, and no immediate effect was expected other than cessation of bleeding inherently due to the presence of the packing. Standard procedures were worked out, after trial and error, in which the type and extent of bleeding

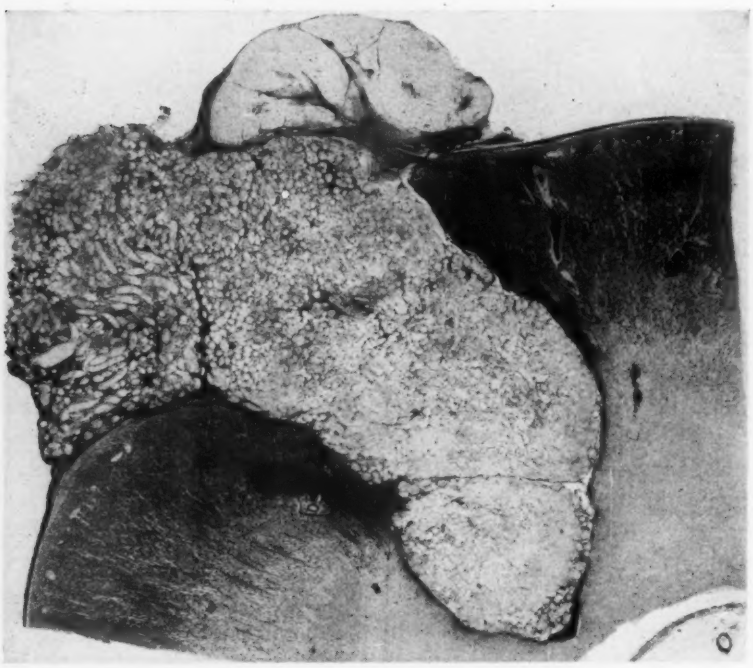

FIG. 1.—Photomicrograph showing oxidized gauze in experimental wound of kidney 48 hours after packing. The gauze is closely applied to the wound surfaces. (Low power.)

could be anticipated, and in which the effectiveness of packing could be estimated. This estimation was, needless to say, based not on any measuring or timing, but on clinical impression. With repeated observations, however, certain unexpected findings were established:

1. The oxidized gauze was easier to pack into a bleeding wound than ordinary gauze. It seemed more pliable, and, when wet with blood, slightly sticky.

2. The oxidized gauze, used dry, was observed to swell when saturated with blood, and this was a second factor which facilitated packing—the gauze easily filling all the irregular crevices in the wound (Fig. 1).

3. The combination of blood and oxidized gauze resulted almost immediately in a dark-brown or black mass and as soon as this discoloration

occurred bleeding usually ceased. (The affinity of the oxidized material for hemoglobin and its effect on this may be seen by immersing a strip of gauze in a test tube of dilute laked blood. Almost immediately the hemoglobin is drawn into the gauze, turning brown, and leaving the solution colorless (Fig. 2).

4. The hemostatic effect appears to depend *not on clotting* within the meshes of the gauze but on the *swelling* of the material and its *sticky character* when blood-soaked, so that the packing itself *takes the place of clot*. We have not studied any possible *direct* effect on the clotting process.

5. Neutralization of the material with calcium acetate resulted in the loss of the above properties, rendering it less effective as an hemostatic.

6. As early as 24 hours after packing, the oxidized gauze was so friable that it broke when an attempt was made to withdraw it, in contrast to ordinary gauze which could be withdrawn, but which, in clean wounds especially, was usually stuck, so that force was necessary for withdrawal. With ordinary gauze, removal was apt to be followed by bleeding, sometimes requiring secondary packing. With oxidized gauze, by 48 hours in an open wound, the gelatinous mass of brown material which represented the blood-soaked packing could be gently scraped away from the wound surface without renewal of bleeding (Fig. 3).

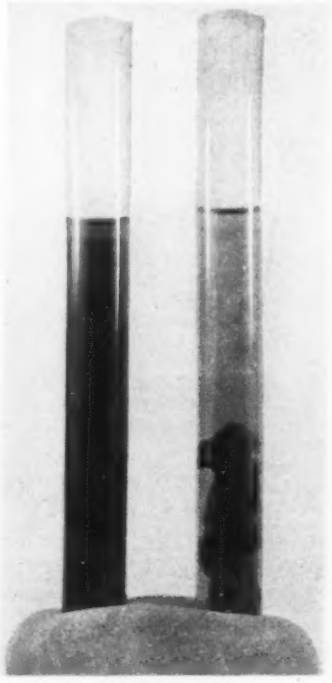

FIG. 2.—Photograph showing oxidized gauze in dilute laked blood—right; control without gauze—left. The control was bright red. The gauze was brown and the supernatant fluid almost colorless.

7. Oxidized gauze, even when not absorbed early, was not invaded by reparative tissue. The foreign body, therefore, was not incorporated in scar to any extent, and scarring was minimal.

8. In serous cavities where a relatively large single mass of material is surrounded by serous membrane, cysts are sometimes formed. These apparently can eventually resorb and have been in general small, not proportional to the amount of gauze used. Such cysts have not been observed in solid viscera or the supporting tissues—connective tissue, muscle, bone. (The work on serous cavities is not complete as regards the study of adhesions, but is reported here to illustrate the tissue reaction to large amounts of gauze).

The observations summarized above are based on experiments in which the wounds were made with the animals under general anesthesia, and with aseptic precautions.

22014
GAUZE PACKING—48 HOURS

Oxidized Gauze Plain Gauze
(Originally same size—10 cm. sq. folded)

FIG. 3.—Gauze packing withdrawn from experimental wounds of kidney after 48 hours. The oxidized gauze was black and friable. The plain gauze was stained with bright red blood.

22053
WOUNDS OF LEFT KIDNEY—5 DAYS

Upper Pole
Gauze—Oxidized
(7 Hours)

Lower Pole
Gauze—Plain

HILUS

FIG. 4.—Autopsy specimen, five days after operation. See Table I, S. P. 22053. At four days an attempt had been made to remove both packings. The oxidized gauze (Eastman OR-1352-B, 7-hour oxidation sample, 13.5-13.8 per cent COOH) was too friable to be withdrawn completely. Through an error, only one of the two strips of plain gauze was withdrawn. No bleeding occurred. Twenty-four hours later the animal was sacrificed. The kidney has been sectioned through the two wounds, showing their size and the gauze packing. On the convex surface of the upper pole there is properitoneal fat.

EXPERIMENTS WITH HEMOSTASIS WITH CLEAN WOUNDS OPEN
(*Kidney, Spleen, and Liver*)

The kidneys were delivered extraperitoneally, through an oblique muscle-splitting incision in the flank. Wounds were made, as nearly as possible similar in the upper and lower poles, by an incision about 1.5 cm. in the capsule, which was deepened by blunt dissection so that the medulla was reached but the pelvis was avoided, and spurting bleeding was obtained. The wound in the upper pole was then packed with oxidized gauze, various

TABLE I

HEMOSTASIS IN OPEN WOUNDS OF VISCERA

(*Oxidized Gauze—Eastman OR-1352-B*)

S.P. No. Animal	Organ	Time Postoper.	Result: Oxidized Gauze	Result: Control Gauze
22020 Dog	Kidney	24 hours	Gelatinous. Easily expressed. No bleeding.	Stuck. Bleeding after removal. Ceased spontaneously.
22025 Dog	Kidney	48 hours	Gelatinous. Scooped out. Followed by thin brown fluid	Stuck. Bleeding after removal. Packed with oxidized gauze.
22059 Dog	Kidney	48 hours	Disintegrated. No free fluid. No bleeding.	Stuck. Bleeding after removal. Packed with oxidized gauze.
22058 Dog	Kidney	48 hours	Disintegrated. Came away with dressing; gush of thin, brown fluid.	Stuck. Bleeding after removal. Stopped spontaneously.
22021 Dog	Kidney	52 hours	Gelatinous. Loose in mouth of wound. No fluid.	Did not control bleeding at operation. Oxidized gauze used.
22052 Dog	Kidney	4 days	Gone from mouth of wound. Dressing dry.	Stuck. Bleeding after removal. Repacked with oxidized gauze.
22053 Dog	Kidney	4 days	Disintegrated. Pressure yielded gelatinous fluid.	Stuck. Only one strip removed. No bleeding. Second strip found at autopsy 5th day.
22025 Dog	Spleen	48 hours	Negligible remnant. (Infected wound). No bleeding.	Stuck. Bleeding after removal, requiring repacking.
22058 Dog	Spleen	48 hours	Gelatinous. (Infected wound). No bleeding.	Stuck. Bleeding after removal. Animal voided blood. Sacrificed.
22059 Dog	Spleen	48 hours	Negligible remnant. (Infected wound.) No bleeding.	Stuck. Moderate bleeding after removal. Animal sacrificed.
22078 Dog	Spleen	48 hours	Loose in wound. No bleeding after removal.	Stuck. Slight bleeding. Animal sacrificed.
22079 Cat	Spleen	48 hours	Gelatinous. No bleeding.	Stuck. Slight bleeding. Animal sacrificed.
22061 Dog	Liver	24 hours	Packing in place. Crumbles. No bleeding.	Stuck. Slight ooze. Animal sacrificed.

samples, and the wound in the lower pole by plain gauze (Fig. 4). In one instance, No. 22021, the kidney was badly traumatized at the lower pole and bleeding could not be controlled by packing with ordinary gauze. Oxidized gauze was, therefore, used and hemostasis secured.

In the case of the spleen exteriorization was three times accomplished through a left lumbar incision at a secondary procedure after nephrectomy of a previously injured kidney. These cases were all infected. Twice a left rectus approach was used. Only one exteriorization of the liver was performed in a survival animal, and this was accomplished through a transverse upper abdominal incision and the liver secured in the wound by tamponade. Repeated observations, however, in anesthetized animals, were made, just prior to death from overdose of anesthesia, of immediate control of

bleeding in all these viscera with various samples of material. The results are noted in Table I.

EXPERIMENTS IN HEMOSTASIS WITH CLEAN WOUNDS CLOSED (*Kidney, Spleen, Liver, Thyroid and Bone*)

Further investigation of the late effects on the tissue of trauma and packing were then undertaken. The wounds were closed.

Kidney.—The technic used for the kidney differed from that employed for open wounds only in that the approach was transperitoneal, through a left rectus incision, and the packing was not allowed to protrude from the viscus, but was cut flush with the surface and a single marking black silk suture was tied loosely over it.

Spleen.—The spleen was also delivered through a left rectus incision. Wounds were then made by excising a rectangular piece of tissue approximately 2 x 1 x 0.3 cm. from the upper surface. Bleeding was always brisk. It was controlled by placing a 10 x 10 cm. square of oxidized gauze, folded, over the defect, and a similar folded sponge of the same material on the opposite surface, securing the two by through-and-through sutures of black silk. This "sandwich" type of packing controlled bleeding quickly. The material used was Eastman OR-1352-B, 7-hour oxidation, and Parke, Davis No. 098630, 5–6 hour oxidation, 13.5–15.8 per cent COOH. The results are noted in Tables II and III.

Liver.—Because of the difficulty of approach and the anaerobic infections which occasionally occur in dogs following liver injuries, this organ was used only five times. Hemostasis was immediately satisfactory in all five cases, whether the gauze was packed into deep wounds in the parenchyma, or used as "sandwich" packing to staunch bleeding from a shallow surface defect. Four of the animals have come to autopsy, at 31, 35, 36, and 42 days, respectively. There was one abscess in which an *hemolytic Staphylococcus aureus* and *C. welchii* were found on culture. This was well walled-off, and there was no infection of the spleen wound in the same animal. In all four the gauze was entirely absorbed.

Thyroid.—Four cases have been studied. The right lobe of the thyroid was split along the convex border, the wound was enlarged by blunt dissection, and oxidized cotton, Parke, Davis No. 098631, packed into the cavity from which bleeding was always brisk. At two weeks the material had not been absorbed (Fig. 10). At four, five, and six weeks the material was entirely absorbed, and the injury was represented by a zone of characteristic phagocytes.

Bone.—Experiments on bone are not complete, due to the length of time required for histologic preparation. Defects have been made repeatedly in the radius, and bleeding was quickly and easily controlled by packing, which was made tight. In such rigid-walled cavities the material could be made to fill the crevices almost like gutta percha. Callus has been shown in some cases roentgenologically, but complete data are not yet at hand.

TABLE II

KIDNEY PACKINGS—TWO EACH CASE—UPPER AND LOWER POLES

S. P. No. Animal	Time Days	Result
22125 Cat	21	Largeiy absorbed. Micros: Remnants. Many phagocytes.
22155 Dog	23	Partly absorbed. Micros: Many phagocytes.
22118 Rabbit	28	Grossly absorbed. Micros: Remnants. Many phagocytes.
22181 Dog	28	Partly absorbed. Micros: Some polymorphonuclears. Many phagocytes.
22248 Dog	29	Largely absorbed. Micros: Remnants. Many phagocytes.
22257 Dog	29	Almost all absorbed. Micros: Remnants. Many phagocytes.
22220 Dog	30	Largely absorbed. Micros: Remnants. Many phagocytes.
22146 Dog	31	Partly absorbed. Micros: Considerable amount. Many phagocytes.
22191 Dog	33	Almost entirely absorbed. Micros: Phagocytes.
22154 Dog	35	Almost entirely absorbed. Micros: Occasional fiber. Phagocytes.
22256 Dog	35	Lower pole—absorbed entirely. Micros: Phagocytes. Upper pole—absorbed very little. Micros: Phagocytes. Giant cells.
22157 Dog	36	Absorbed. Micros: Rare fiber in one pole. Phagocytes.
22214 Dog	37	Absorbed. Micros: Rare fiber in one pole. Phagocytes.

TABLE III

OXIDIZED GAUZE "SANDWICH" PACKING OF WOUND OF SPLEEN

S. P. No. Animal	Time Days	Result
22125 Cat	21	Omental adhesions. Gauze gelatinous. Micros: Phagocytes. Giant cells. Cicatrix.
22311 Dog	22	Omental adhesions. Some gross gauze present. Micros: Phagocytes. Giant cells. Polys. N.B. This animal had a large amount of gauze also packed in the pelvis.
22312 Dog	22	Omental adhesions. Some gross gauze present. Micros: Phagocytes. Giant cells. Polys. N.B. This animal had a large amount of gauze also packed in the pelvis.
22155 Dog	23	Omental adhesions. A little gauze in wound. Micros: Some gauze both sides. Phagocytes. Few giant cells.
22181 Dog	28	Omental adhesions. No gross gauze. Micros: Gauze remnants. Phagocytes. Giant cells.
22248 Dog	29	Omental adhesions. No gross gauze. Micros: Few fibers both sides. Phagocytes. Many giant cells.
22257 Dog	29	Omental adhesions. No gross gauze. Micros: No gauze. Few phagocytes. Slight cicatrix.
22220 Dog	30	Omental adhesions. No gross gauze. Micros: Occasional gauze fiber. Phagocytes.
22146 Dog	31	Omental adhesions. Bulk of gauze gone. Scarring. Micros: Phagocytes and polymorphonuclear leukocytes. (Liver abscess in this case.)
22191 Dog	33	Omental adhesions. No gross gauze. Micros: Remnants. Phagocytes. Moderate cicatrix.
22154 Dog	35	Omental adhesions. No gross gauze. Micros: Few fragments. Phagocytes. Marked cicatrix.
22256 Dog	35	Omental adhesions upper and under surface. No gross gauze. Micros: Remnants. Phagocytes. Giant cells.
22157 Dog	36	Omental adhesions very delicate. No gross gauze. Micros: Gauze fragments only upper surface. Phagocytes.
22214 Dog	37	Omental adhesions. No gross gauze. Micros: No gauze. Few phagocytes. Slight cicatrix.
22356 Dog	40	Omental adhesions. No gross gauze. Micros: Tiny remnant. Phagocytes.

EXPERIMENTS WITH GAUZE SPONGES WRAPPED IN OMENTUM

A sponge was made of a 10 x 10 cm. square of oxidized gauze, and this was placed on the surface of the omentum. In most instances the sponge was dry. In a few cases it was first wet with the animal's blood. The omentum was then folded over it and tacked in place with two marking silk sutures. The results are noted in Table IV.

It will be seen from study of these tables that the time of absorption is variable. There are several possible factors in this connection which may all operate together, but which may be discussed separately.

1. Amount of Material: Since disappearance of the material depends, at least in part, on solution, large amounts of gauze packed into small spaces might not readily be penetrated by tissue fluids, and absorption would be delayed. Penetration by phagocytes would also be slower the greater the bulk of the foreign body.

2. Degree of Injury: This is difficult to evaluate, but obviously the integrity of the circulation to the part would influence rapidity of absorption.

3. Amount of Blood Present: This would at least add to the bulk of material to be absorbed.

4. Nature of the Tissue: This is illustrated by the fact that in the kidney considerable delay was repeatedly found, whereas, in the omentum, for instance, absorption was, in general, more rapid. This may possibly be related to the lower p_H of the tissue fluids in the kidneys of laboratory animals (dogs and cats). On one determination upon homogenized kidney tissue of a dog the p_H was 6.63.

5. Lack of Uniform Degree of Oxidation: Occasional fibers of gauze remaining when the bulk is absorbed may, perhaps, contain a lower percentage of carboxyl groups.

These variables are all reflected in the gross and microscopic findings in the tissues which have been in contact with the material. In our earlier report in the ANNALS we submitted photomicrographs of the reaction of various tissues at varying intervals after operation. The amounts used were small, and a deliberate attempt was made to avoid all unnecessary injury and bleeding. In the present series, except in the omental implants, the tissues have been deliberately traumatized, and the gauze used for hemostasis. As was expected from our earlier experience there has been no acute inflammatory reaction to the material itself. There have been, however, phagocytic reactions, of varying degree. Where no great amount of hemosiderin is present, the phagocytes show large basophilic droplets in the cytoplasm. Almost no granulation tissue is present around the foreign body, and there are only rare infiltrating cells other than phagocytes. A characteristic zone is found, of typical large phagocytes showing intense basophilism, almost diagnostic for the material. Less detailed studies have been made with other materials, and while phagocytes are found in some instances, none has had this particular appearance. These variations and the histologic findings are illustrated in photomicrographs (Figs. 5–10).

TABLE IV

OXIDIZED GAUZE SPONGE IN OMENTUM

(Square 10 x 10 cm. Folded)

(Eastman OR-1352-B and Parke, Davis 098630)

S.P.No.	Time	Surrounding Omentum	Character of Material	Microscopic Findings
21591 Cat	6 hours	Not inflamed. Not adherent.	Easily cut with knife.	Rare polys. No fibrin.
21630 Cat	22 hours	Not inflamed. Not adherent.	Slightly gelatinous.	No polys. Slight edema. No fibrin.
21576 Cat	24 hours	Slightly injected. Not adherent.	Slightly gelatinous. Culture sterile.	Scattered polys. No fibrin.
21579 Cat	30 hours	Not inflamed. Not adherent.	Light tan, soft, fibrillar. Culture sterile.	No reaction.
21568 Cat	3 days	Thickened, cystic cavity.	Mostly clear fluid. Little brown jelly. Culture sterile.	Polys. Fibroblasts.
21572 Cat	3 days	Thickened; cystic cavity.	Cloudy fluid. Culture sterile.	Fibrin. Polys. Fibroblasts.
21858 Dog Dog	3 days	Fibrinopurulent peritonitis. (Previous appendicectomy).	Light tan, gelatinous, fibrillar.	Pus.
21590 Cat	4 days	Thickened; cystic cavity.	Clear fluid. Culture sterile.	Fibrin. Polys. Fibroblasts.
21600 Cat	5 days	Thickened; cystic cavity.	Cloudy fluid. Culture sterile.	Fibrin. Polys. Fibroblasts.
21886 Dog	7 days	Thin-walled, cystic cavity.	Clear fluid slightly blood-tinged. Few fibers.	Lining of phagocytes. No polys. Fibroblasts.
21887 Dog	10 days	Thick-walled cyst. Little inflammation.	Thick, white fluid. Culture coagulase-pos. Staphylococcus.	Polys. Phagocytes. No fibroblasts.
21899 Dog	14 days	Thickened; cystic cavity.	Brown, cloudy fluid. Culture *Esch. coli*.	Few polys. Phagocytes. Little fibroplasia.
21905 Dog	18 days	Thick-walled, cystic cavity.	Thick, white fluid. Not cultured.	Rare polys. Lining of phagocytes.
22125 Cat	21 days	Transparent cyst, 2 cm.	Clear fluid.	Few fibers, phagocytes. No polys.
22155 Dog	23 days	Dark red, soft mass, 1.2 cm.	Soft solid on section.	Fragments of gauze. Phagocytes.
22056 Cat	28 days	Thickening 4 mm.	Entirely absorbed.	Characteristic phagocytes.
22057 Dog	28 days	Thickening 3 mm.	Entirely absorbed.	Characteristic phagocytes.
22181 Dog	28 days	Transparent cyst, 2.5 cm.	Thin, brown fluid and jelly.	Lining composed of phagocytes.
22248 Dog	29 days	Red-brown zone of thickening 1 cm.	Center friable.	Considerable gauze. Phagocytes.
N.B. This sponge had been soaked in blood.				
22257 Dog	29 days	Slight thickening, 0.8 cm.	Entirely absorbed.	No gauze. Characteristic phagocytes.
N.B. This sponge had been soaked in blood.				
22220 Dog	30 days	Tiny zone of thickening marked by suture.	Entirely absorbed.	No gauze. Few phagocytes.
22146 Dog	31 days	Slight omental thickening marked by suture.	Entirely absorbed.	No gauze. Characteristic phagocytes.
22191 Dog	33 days	Thickening, 0.5 mm. marked by suture.	Entirely absorbed.	No gauze. Characteristic phagocytes.
22065 Dog	35 days	Marking sutures found.	Entirely absorbed.	Phagocytes. No polys.
22066 Cat	35 days	Marking sutures found.	Entirely absorbed.	Phagocytes. No polys.
22154 Dog	35 days	Light brown zone of thickening, 1 cm.	Entirely absorbed.	No gauze. Thick zone of phagocytes.
22256 Dog	35 days	Smooth-walled cavity	Brown mass, 5 x 5 x 7 mm.	Fragments of gauze in fluid with some blood.
22157 Dog	36 days	Brown thickened zone 3 x 1 cm.	Entirely absorbed.	No gauze. Phagocytes.
22214 Dog	37 days	Transparent cyst, 2.5 cm.	Clear fluid.	Few fibers, fluid. Characteristic phagocytes.
22356 Dog	40 days	Brown thickening.	Entirely absorbed.	Phagocytes. Scar.

CLINICAL INVESTIGATION

Clinical trial of the material was delayed until the formaldehyde sterilized material which was available had been checked for sterility and tested for irritating qualities in the tissues. It has been used for hemostasis in 17 cases. In four of these packing of some sort was imperative and, in two of the

TABLE V

HEMOSTASIS IN CLINICAL CASES WITH SOLUBLE GAUZE AND COTTON

Case	Hist. No.	Date	Surgeon	Source of Bleeding	Closure	Result
1	633513	4/13/44	Stookey	Internal carotid.	Closed.	Sinus lower angle 6th day. Closed 30 days. No infection.
2	741353	4/18/44	Whipple	Gallbladder bed.	Drained.	Tube out 9th day. Healed 14th day.
3	741879	4/22/44	Humphreys	Liver surface, through diaphragm.	Intercostal drainage 48 hours.	Healed 7th day.
4	627664	5/1/44	St. John	Incisional biopsy liver.	Closed.	Healed *per primam*.
5	639170	5/4/44	Humphreys	Intercostal vein. Sympathectomy.	Closed.	Hematoma, followed by pleurisy with effusion.
6	706699	5/6/44	Scudder	Metatarsal. Amputation toe.	Open. Infected.	Hemostasis satisfactory. Removed 3rd day. No bleeding.
7	742421	5/11/44	Humphreys	Cervical lymph node. Biopsy: Ca.	Closed.	Hemostasis satisfactory. Healed *per primam*.
8	744514	5/12/44	Humphreys	Sternum. Biopsy: Leukemia.	Closed.	Hemostasis satisfactory. Healed *per primam*.
9	738341	5/13/44	Harvey	1. Plantar abscess. Drainage.	Open. Infected.	Hemostasis satisfactory. Removed 24 hours. No bleeding.
		6/4/44	Harvey	2. Plantar abscess. Revision of drainage.	Open. Infected.	Hemostasis satisfactory. Removed 3 days. No bleeding.
10	733473	5/13/44	Auchincloss	Gallbladder bed.	Drained.	Hemostasis satisfactory. Slight bleeding 9th day. Cause? Biliary fistula 2nd to 17th day.
11	743824	5/22/44	Whipple	Spleen collaterals. Splenectomy.	Closed.	Healed *per primam*.
12	Beth David 44/1849	5/24/44	Bancroft	Scar tissue leg. Releasing incision 20 cm. long down to muscle.	Open. (Leg ulcers)	Hemostasis satisfactory. Removed 3rd day. No bleeding. Wound ready to graft 16th day.
13	737472	5/25/44	Hanford	Liver. Punch biopsy.	Closed.	Hemostasis satisfactory. Healed *per primam*.
14	747716	5/26/44	Whipple	Gallbladder bed.	Closed.	Hemostasis satisfactory. Healed *per primam*.
15	747707	5/27/44	Blakemore	Periaortic. Occlusion aortic aneurysm, abdominal.	Closed.	Hemostasis satisfactory. Healed *per primam*. Some ecchymosis.
16	747805	6/3/44	Blakemore	Periaortic. Wiring aortic aneurysm, abdominal.	Closed.	Died, cardiac failure 24 hours. No autopsy.
17	738386	6/3/44	Mount	Sagittal sinus. Opening sagittal suture.	Closed.	Hemostasis satisfactory. Wound healed 4th day.

four, wounds were closed which otherwise would have had to be left open and from which the packing would subsequently have had to be withdrawn. In three biopsy wounds—two liver and one sternal marrow—it took the place of muscle, which would otherwise have been used, and was considered fully as satisfactory, if not more so. In three oozing gallbladder beds it was a convenience but probably not a necessity. The other cases constitute scattered clinical trials. The complete list is to be found in Table V.

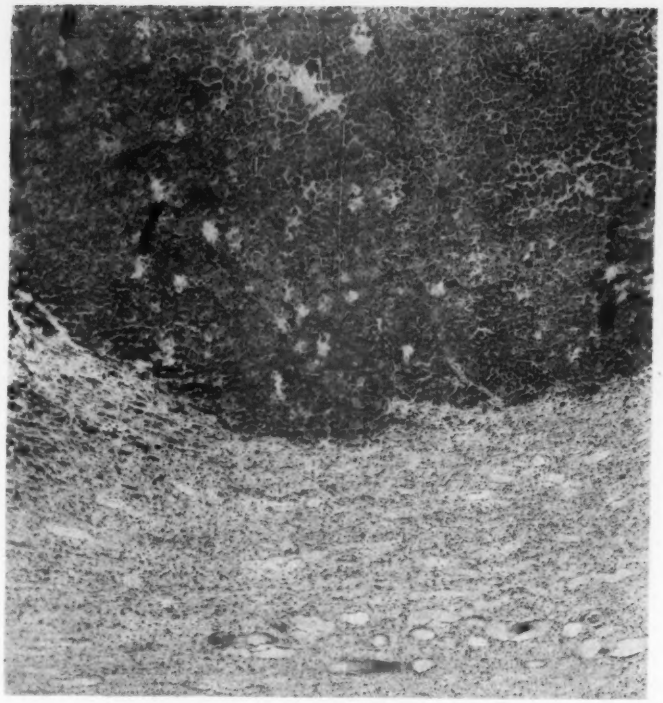

FIG. 5.—S. P. No. 22146: Photomicrograph 31 days after operation, showing broad zone of typical phagocytes immediately adjacent to kidney parenchyma, with almost no granulation tissue. (Low power.)

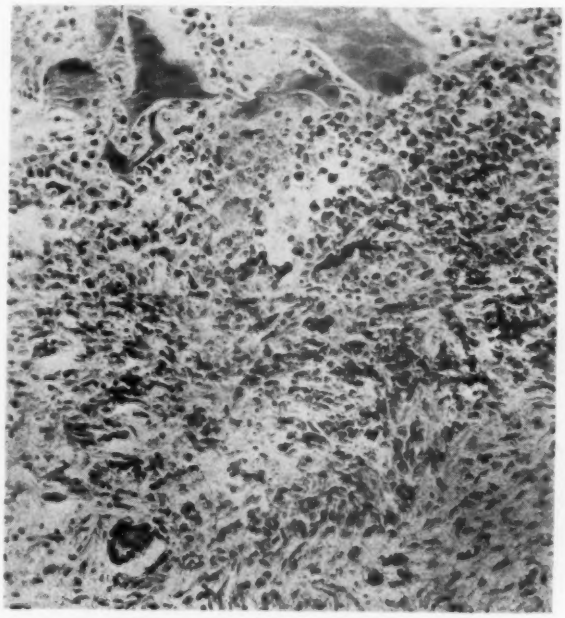

FIG. 6.—S. P. No. 22220: Photomicrograph showing remnants of oxidized gauze, above, persisting in kidney wound 30 days after packing. In this case few phagocytes are seen, and multinucleated foreign body giant cells are present, with considerable cicatricial tissue.

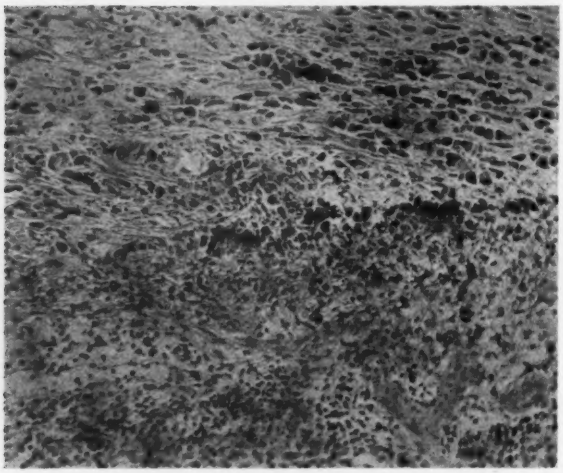

FIG. 7.—S. P. No. 22220: Photomicrograph showing site of "sandwich" packing on surface defect of spleen 30 days after operation. The spleen shows almost no scarring. There are typical phagocytes in scar tissue, above, binding the omentum to the spleen. The gauze has been entirely absorbed.

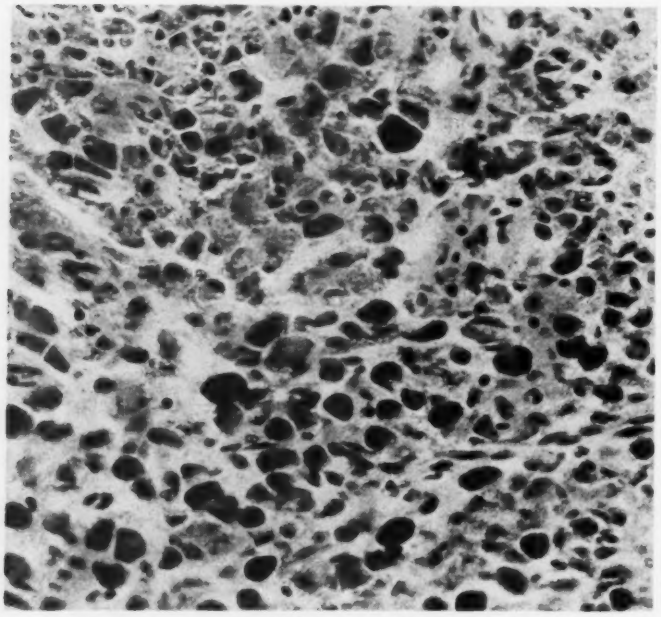

FIG. 8.—S. P. No. 22220: Photomicrograph showing typical phagocytes in the very small zone of thickening in the omentum 30 days after oxidized gauze sponge implant. No cyst was formed. The gauze was completely absorbed.

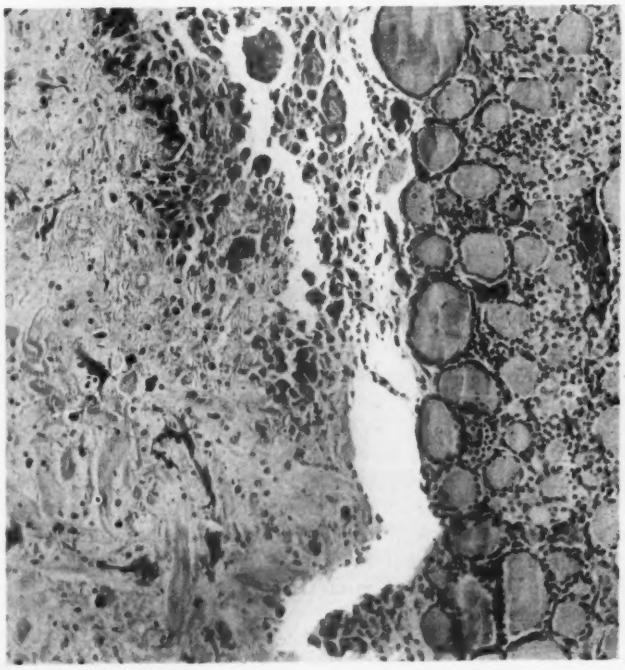

FIG. 10.—S. P. No. 22312: Photomicrograph showing oxidized gauze in thyroid, 14 days after operation. In some parts—left, the gauze lies, except for artefact, against thyroid parenchyma with almost no reaction. On the right there is a zone of phagocytes between the packing and the thyroid.

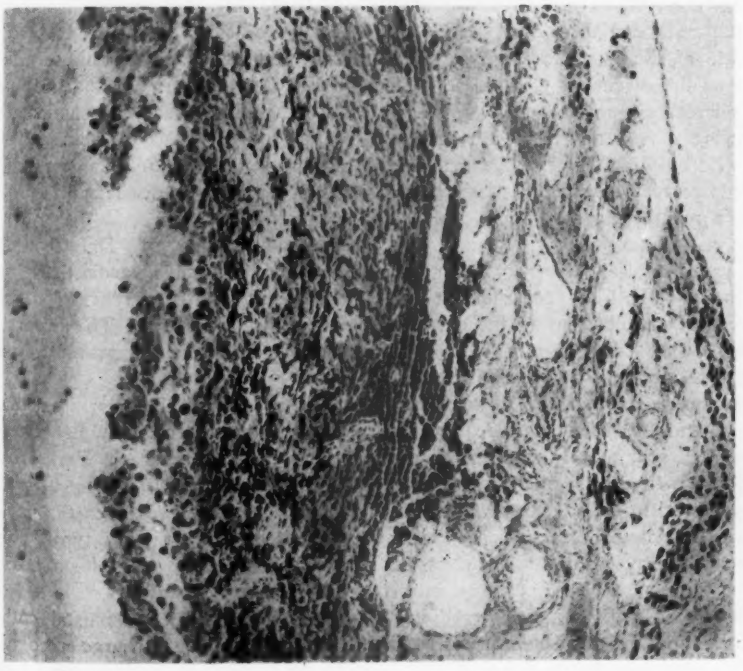

FIG. 9.—S. P. No. 22214: Photomicrograph showing wall of omental cyst 2.5 cm. in diameter 37 days after oxidized gauze sponge implant. The surface of the omentum is shown as the lower border. There is some fibrosis, but the wall is thin. The lining appears above as several layers of phagocytes without granulation tissue. The fluid content shows few cells.

It will be seen in the table of clinical cases that there is one case in which hemostasis was obviously not secured and which was complicated by an hematoma and pleurisy with effusion. This case, together with the four cases in which packing of some sort was imperative, two closed and two open, are analysed in detail.

ANALYSIS OF CLINICAL CASES

Case 1.—History No. 633513: M. D., female, white, age 38. Dr. Byron Stookey. Four previous attempts by other surgeons to relieve pain by division of the sensory root of the right trigeminus. Persistence of symptoms.

Operation.—April 10, 1944: Fifth craniotomy. Scar tissue was encountered which, when slightly manipulated after root section had been completed, gave way, and sudden bleeding occurred, thought to come from the internal carotid. This was controlled by vaselined gauze packing. The wound was drained at the lower angle.

Course.—There was no febrile reaction following this procedure.

Operation.—April 13, 1944: Wound opened. Packing removed. There was fresh bleeding of the same type as at the original procedure three days earlier. This was controlled by packing with formaldehyde sterilized oxidized gauze, Parke, Davis 6-hour oxidation No. 098630. Three strips were used, 8 x 6 cm. each, folded in four. The first strip was impregnated with 1 cc. of sodium penicillin 5,000 units. Bleeding was completely controlled by the first two pieces of packing. The third piece was used as reinforcement, but perhaps added unnecessarily to the bulk—something probably to be avoided. The wound was closed.

Course: Patient ran no fever. There was swelling at the lower extremity of the wound, the site of the original drainage, first observed at the first dressing on the fourth postoperative day, when all sutures but one were removed. There was no redness in the swollen area, which was in the anesthetic zone following root section.

On the sixth day there was spontaneous discharge of thin, brown fluid from the lower angle of the wound, with particles of black, oxidized gauze. Culture of the discharge on the seventh day yielded organisms of the *B. subtilis* group and coagulase-negative micrococci—no pathogens. The sinus continued to drain small amounts of sticky fluid showing almost no cells on smear. On May 1, 1944, 17 days after secondary packing with oxidized gauze, the patient had a small, unhealed, granulating area in the lower angle of the wound with practically no residual swelling or discharge. On May 15, 1944, a month after operation, the wound was entirely healed.

Case 3.—History No. 741879: N. Y., male, Japanese, age 55. Dr. George H. Humphreys. Atypical history. Roentgenograms showed possible mediastinal mass.

Operation.—April 22, 1944: Right lower lobe lobectomy for carcinoma of lung. There were many adhesions to the chest wall and to the diaphragm. The lower lobe was largely occupied by a tumor which, on quick frozen-section, appeared to be a carcinoma. Lobectomy was, therefore, carried out.

In this procedure part of the diaphragm was resected, and the liver immediately beneath was torn. There was bleeding which could not be controlled by ligature, and which required packing. Five pieces of oxidized gauze, 8 x 6 cm. each, Parke, Davis No. 098630 sterilized by formaldehyde, were folded to form a compress about 4 x 2 cm. This was applied to the surface of the liver, and the diaphragm closed over the packing with three interrupted black silk sutures. The oxidized gauze rapidly turned black, and hemostasis was considered satisfactory. Sulfadiazine powder was blown into the cavity and the wound closed, with an intercostal catheter for drainage.

Course.—The patient had a gratifyingly smooth course. The intercostal catheter was removed on the third postoperative day, with no unusual discharge recognized. All stitches were removed on the sixth postoperative day, and the wound appeared healed.

The patient was afebrile from the sixth postoperative day. On May 1, 1944, the ninth postoperative day, roentgenograms showed some fluid at the right base, less, if anything, than one would expect under the circumstances.

Case 5.—History No. 639170: A. P., male, white, age 36. Dr. George H. Humphreys. A case of essential hypertension admitted for a left dorsolumbar sympathectomy, to be done in two stages.

Operation.—May 4, 1944: Through a paravertebral hockey-stick incision, cutting the diaphragm and dissecting the pleura forward off the mediastinum, the sympathetic chain was exposed along the lower dorsal vertebrae. Bleeding was encountered from the intercostal vein in the ninth interspace, which could not be controlled by clamping because of poor exposure. Bleeding was controlled by one 4 x 8 cm. oxidized gauze sponge, Parke, Davis No. 098630, folded into a square approximately 1.5 cm. square, which was pressed into the intercostal space and held in place digitally until the gauze had become black and bleeding had been controlled. For a period of about 15 minutes thereafter no obvious bleeding occurred from the site. The gauze remained stuck without suture. Wound closed without drainage.

Course.—At the first dressing, seven days after operation, the wound appeared well healed. All sutures were removed on the eighth day. The patient was never entirely afebrile, but was apparently doing well until the fourteenth day, when he began to run a spiking temperature, to complain of pain in the posterior part of the wound, and to cough. Roentgenograms of the chest on this day showed pleural effusion, and swelling was also noted in the posterior portion of the wound. Aspiration, extrapleural in the eighth interspace, yielded 40 cc. of thick bloody fluid. On the nineteenth day a second aspiration in the tenth interspace, extrapleural, yielded 300 cc. of ropy, slightly purulent old blood, with a faint fishy odor.

Thoracenteses on the twenty-seventh, thirty-second, and thirty-fourth postoperative days yielded 1,350, 1,350, and 250 cc., respectively, of clear, slightly blood-tinged pleural fluid. The patient was given sulfadiazine. On the thirty-fourth day the extrapleural collection was tapped again, and 150 cc. of thick, grumous, brownish-red fluid was obtained. All cultures were negative, but on the thirty-fourth day the extrapleural pus showed an *hemolytic Staphylococcus aureus* on culture.

COMMENT.—This case is given in detail because it is a failure in hemostasis. Doctor Humphreys is now of the opinion that with bleeding of this magnitude the gauze should have been held in place by suture, and that the hematoma cannot be attributed to a failure of the material but to an error in the way in which it was used. The interpretation of this complication is not altogether clear, the febrile reaction having been somewhat greater than one would expect with a simple hematoma, even though large and a sterile pleural effusion. Very possibly the sulfadiazine therapy was responsible for the failure of growth of organisms, and the infection, in view of the repeated aspirations and the initial absence of organisms or pus, should probably not lead to suspicion that the gauze was contaminated.

Case 9.—History No. 738341: N. C., female, white, age 64. Dr. H. D. Harvey. A case of infection of the foot of three months duration in a woman with arteriosclerosis and mild diabetes. In an effort to save at least part of the foot repeated attempts were made to secure adequate drainage. This included removal of the first three toes, and wide opening down to the plantar fascia. The infection was not completely controlled and although there was considerable healing, a sinus led to sloughing plantar fascia and flexor tendons.

Operation.—May 13, 1944: Revision of drainage. The sinus tract was laid open

down to the deep slough. The granulation tissue was edematous and there was profuse bleeding from many small vessels. Oxidized gauze, Parke, Davis No. 098630, was packed into the wound. Bleeding continued, but stopped when pressure was applied. A pressure dressing, therefore, was used.

Course.—May 14, 1944: First day postoperative. The gauze was gelatinous and came away readily. There was no further bleeding. The slough continued to separate, but in the course of three weeks the sinus had again closed prematurely and drainage was inadequate.

Operation.—June 5, 1944: Revision of drainage. The sinus was opened. There was dense scar tissue around it from which bleeding was brisk. One vessel of considerable size was encountered and transfixation and ligature were not feasible. Packing was, therefore, imperative. Oxidized gauze, Parke, Davis No. 098630, was used, and the wound was filled to the surface with gauze which was allowed to overlap the skin edges slightly to prevent sticking of the dressing.

Course.—June 6, 1944: First day postoper. The gauze was black and the surface dry. There was no marked redness around the wound. The patient said she had had pain during the night. The outer dressing was practically dry. The packing was not disturbed.

June 7, 1944: Second day postoperative. Dressing. The gauze was still dry on the surface and could be removed almost in one piece. A few fragments remained in the wound. These could be picked up with forceps, and although somewhat gelatinous, still had fibrillar structure. No bleeding followed removal of the gauze. The wound edges had been kept apart satisfactorily for the 48 hours. There was no retained exudate in the wound, although there was slough, as expected, in the depths.

Case 13.—Beth David Hosp. No. 44/1849: A. C., male, white, age 55. Dr. Frederic W. Bancroft.

History.—In November, 1942, the patient had a bilateral herniorrhaphy. After discharge from the hospital he developed pain in the right knee and the whole leg became swollen, presumably a phlebitis. After the pain subsided, the leg remained swollen and ulceration began June, 1943.

Past History.—Neisserian infection, 1939. Otherwise irrelevant.

Physical Examination.—Right leg markedly swollen below the knee with a wide zone of brown discoloration and superficial ulceration, two ulcers as large as 5 cm. each. Urine analysis showed no sugar. Blood sugar 100 mg. per cent, W. B. C. 11,800, polys. 64 per cent.

The patient was treated by rest, elevation, and dressings for ten days preoperatively.

Operation.—May 24, 1944: Ligation of saphenous bulb. Release of scar tissue. An incision about 20 cm. was made on the medial aspect of the calf and deepened through dense scar tissue through the deep fascia and the sheath of the muscles. The scar tissue was exceedingly thick, and there was no marked gaping until the deep fascia was cut. The wound then gaped widely, and obvious bleeders were controlled by catgut ligature. There was ooze from all the surfaces of the scar tissue and, accordingly, four pieces of oxidized gauze, Parke Davis D-2340-C, were laid on the wound surface. As a test of the material two cotton pledgets, Parke, Davis D-2339-C, were placed in the lower angle of the wound. It was Doctor Bancroft's impression that the material was hemostatic.

Vaselined gauze packing was then placed in the wound and a light pressure dressing applied. Neither the packing nor the pressure was so much as Doctor Bancroft has used in the previous dozen or so cases of this operation of his own devising.

Course.—May 25, 1944: First day postoper. Doctor Bancroft reported by telephone that the patient's bandages were dry in contrast to the usual postoperative oozing of previous cases.

May 27, 1944: Third day postoperative. First dressing. There was, according to Doctor Bancroft, less blood on the dressing than usual. The gauze was soft, somewhat slimy on the under surface, and could be scooped out of the wound. Nowhere was it stuck, and no bleeding occurred except where the vaselined gauze was stuck on the wound edges. It would have been better to cover the wound edges with the oxidized gauze. Doctor Bancroft felt that the hemostasis had been unusual, and the dressing satisfactory. The wound looked somewhat brown. Vaselined gauze dressing.

May 30, 1944: Sixth day postoperative. Wound still brownish. Little exudate.

May 31, 1944: Seventh day postoperative. Wound still brownish. Little exudate. Acriflavine wet dressing. Dressed thereafter q.2.d. with acriflavine. Wound ready for grafting June 9, 1944, 16 days postoperative.

COMMENT.—In previous cases of leg ulcer and deep scarring, which Doctor Bancroft has treated by one or more releasing incisions, he has found the wound suitable for grafting some time between the tenth and twenty-first postoperative day. This case, ready for grafting on the sixteenth postoperative day, is in line with the others. In his opinion, use of the oxidized gauze facilitated hemostasis and did not hinder repair.

SUMMARY

This report is submitted at this time in the hope that further clinical trial of the material will be made in other hospitals, so that, if it proves useful, its availability to the armed forces may be expedited. It appears to have sufficient hemostatic properties when used dry so that combination with thrombin is probably unnecessary, possibly undesirable. It is hoped that the investigators who are familiar with the control of hemorrhage with thrombin and cellulose as a carrier (Putnam, Ingraham and Bailey, Cronkite, Deaver, and Lozner), will try the cellulose without the thrombin, as the reverse has already been tried. Possibilities of impregnation of the material with antibacterial substances naturally suggest themselves. This field needs further study, but our own preliminary work with penicillin suggests an incompatibility. Work is still in progress on the development of nonirritating membranes, and absorbable suture, or at least ligature, material. It is too early to evaluate these results.

At the risk of being pedantic, we close with a warning. This material, even though soluble and *relatively* nonirritating *is a foreign body* in the tissues and remains as such often for several days. It should be used, at least in wounds which are closed without drainage, in as small quantity as possible. It is not a substitute for meticulous surgery, and surgical principles must not be violated in its use.

We are indebted to Miss Daisy Mapes, R.N., for her assistance in all of the animal experimental work, her close scrutiny of the material, and the results of its application.

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LEIOMYOMA OF THE JEJUNUM

INTERMITTENT MELENA OF FOURTEEN YEARS DURATION, AND FATAL HEMORRHAGE

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LEIOMYOMA OF THE SMALL INTESTINE is uncommon. Raiford,[15] in 1931, collected 82 cases of small bowel tumors from the records of the Johns Hopkins Hospital. Only three cases of this total were leiomyomata, two of these occurring in the jejunum and one in the ileum. In a later report, Raiford,[16] from a study of the findings in 11,500 autopsies and 45,000 surgical pathologic specimens, was able to find a total of 986 cases of tumors, both benign and malignant, of the gastro-intestinal tract. Of these, tumors of the small intestine constituted 8.9 per cent, the benign tumors of the small intestine making up 23.8 per cent of all the benign neoplasms of the gastro-intestinal tract.

Rankin and Newell,[17] in 1933, reported 95 instances of neoplasms of the small bowel; 35 of these were benign, 11 of this group being leiomyomata. A year later, Moore and Schmeisser,[13] in a review of the literature, were able to cull only 46 case reports of small intestine leiomyomata. Of this group, nine occurred in the duodenum, 15 in the jejunum, 19 in the ileum, and the site in four instances was not specified; in only one case were multiple tumors present. In 1937, Smith[19] was able to collect 513 cases of leiomyomata of the gastro-intestinal tract. Of these, 50 occurred in the esophagus, 321 in the stomach, 109 in the small intestine, and 33 in the colon. He found, in reviewing the protocols of 36,000 autopsies at the Philadelphia General Hospital, 33 cases of gastro-intestinal tract leiomyomata, eight of which arose from the small bowel. Two years later, Horsley and Keasbey[7] reported 15 additional cases of leiomyomata of the small bowel. Morison,[14] in an analysis of the biopsy and autopsy material of 13,139 patients at Queen's University, at Belfast, found 21 benign tumors of the small intestine, of which two were leiomyomata of the ileum. In 1942, Weber and Kirklin[20] analyzed the material at the Mayo Clinic over a 32-year period and gathered a total of 108 malignant small bowel tumors and 41 benign neoplasms of the small intestine; of the latter group, myomata constituted 14 cases, eight of these being found in the duodenum, four in the jejunum, and two in the ileum. Since then, additional case reports have appeared sporadically in the literature.[2, 6, 8, 10, 18]

There is no marked sex predilection for leiomyomata of the small bowel, although, as for tumors in general, males may be slightly in the fore.[16] The majority of benign tumors of the small bowel occur between the ages of 30 and 40,[17] but the age incidence is wide, ranging from 13 to 79.[13, 16] One case in a child, age two, has been reported.[12]

In size, leiomyomata of the small intestine may vary from that of a pea to that of a large grapefruit. A tumor weighing 1,500 grams has been reported.[4]

Leiomyomata of the small bowel are most common in the ileum. The next most frequent site is the jejunum, while the duodenum is only rarely affected.[13, 16]

Pathologically, leiomyomata of the small intestine have been classified, according to site in the bowel wall, as principally submucosal or principally subserosal, 70 of the 109 cases of Smith[19] falling into the latter group. Microscopically, leiomyomata are made up of whorls and interlacing bundles of smooth muscle cells, a varying amount of fibrous supportive stroma being present. Necrosis, hyaline degeneration, and hemorrhage into the tumor mass have been described.[16]

The incidence of malignant change in leiomyomata of the small intestine seems to be surprisingly high. According to Klopp and Crawford,[11] malignant change occurs in from 15 to 20 per cent of small intestinal myomata, and Smith[19] states that metastases or recurrences have occurred in 16 per cent of those leiomyomata of the subserosal type; no metastases, however, have been reported in leiomyomata of the submucosal variety. These findings are in striking contrast to the relatively low incidence of sarcomatous change in the histologically comparable leiomyofibroma of the uterus, which is between somewhat less than 1 per cent[3] and 2.5 per cent.[5]

Clinically, not all myomata of the small intestine give rise to symptoms. In Raiford's series of benign small bowel tumors,[16] 46 per cent were encountered as an incidental finding at autopsy, and only 18 of the 35 cases catalogued by Rankin and Newell[17] had symptoms referable to the lesion. However, of the 109 cases reported by Smith,[19] in only 15 instances was the lesion discovered as an incidental finding at operation or autopsy, the other cases having given rise to definite clinical complaints.

The two outstanding clinical features of the reported cases of leiomyomata of the small bowel are mechanical intestinal obstruction and enterorrhagia. In those tumors which are for the most part submucosal, the commonest presenting finding is intestinal obstruction secondary to intussusception, repeated episodes being not uncommonly observed. Intestinal obstruction was observed in 27 of the 39 cases of myomata of the submucosal variety reported by Smith.[19] Of those tumors which extend chiefly subserosally, the principal clinical feature is, in most instances, gastro-intestinal hemorrhage, repeated episodes of melena being found in an appreciable number of instances. Smith[19] reported gastro-intestinal hemorrhage in 22 of his 70 cases of myomata of the subserosal type, and hemorrhage has been prominent in cases reported by others.[1, 4, 9, 10, 13] Other less frequent clinical manifestations of small intestinal myomata are evidences of peritoneal irritation secondary to acute necrosis of the tumor mass or volvulus,[4] the presence of a palpable mass in the abdomen,[12, 14, 19] recurrent ulcer-like distress,[17, 18, 19] frank peritonitis due to rupture,[4, 19] and vague, nondescript indigestion.[19]

Roentgenologic examination, in many instances, is of assistance in the

diagnosis of tumors of the small bowel, but this is by no means true in all cases. There are several reasons for the failure in some cases to diagnose the presence of a small intestinal tumor roentgenographically. Perhaps the most important of these is the failure of the clinician to suspect the presence of a lesion of this type, and, as a consequence, the roentgenologist, not being forewarned, does not look for evidence of the lesion with sufficient care or sufficient persistence. Secondly, subserosal tumors, which accounted for two-thirds of the cases of myoma reported by Smith,[19] are unlikely to produce a marked subtraction defect in the silhouette of the barium-filled small bowel. Thirdly, due to the extensive overlapping of small bowel shadows, a defect, even if present, may easily be overlooked. Repeated progress-meal studies and, in some cases, the introduction of barium directly into the jejunum through a tube are prerequisites for adequate roentgenologic visualization of small intestinal neoplasms. If obstruction due to a tumor of the small bowel is present, plain films of the abdomen will reveal the usual roentgenologic evidences of dynamic ileus, and in those cases of colonic involvement by an intussuscepting mass in the small intestine barium enema studies are of value.

We have recently had the opportunity to study a patient with a leiomyoma of the jejunum who had 20 known episodes of melena over the course of 14 years. This represents, to our knowledge, the most protracted history of episodic bleeding and the greatest number of individual hemorrhages to be reported in a case of leiomyoma of the small intestine. We are, therefore, describing this case in detail.

Case Report.—M. P., a Jewish male, age 53, was first admitted to the Graduate Hospital under the care of Dr. H. L. Bockus, November 30, 1941, complaining of the passage of several tarry stools that morning. His history dated back to 1930 when, for the first time, he noticed that for a period of three or four days his stools were black. Four months later, a similar episode occurred. Roentgenologic examination at that time revealed no evidence of ulceration in the upper gastro-intestinal tract. The patient did well for a period of eight months before melena once more was noted. A second barium progress-meal revealed changes which were somewhat suggestive of peptic ulcer. During the following two years the patient experienced two more episodes of bleeding. During this time he never presented any clinical complaints suggestive of active peptic ulcer. However, in 1933, a gastro-enterostomy was performed, although, at operation, no ulcer of the stomach or duodenum could be demonstrated. Five months later melena of several days duration again appeared, and during the next two years this recurred sporadically at intervals of five to six months. In 1936, the patient developed marked melena, which was associated with the vomiting of dark brown material. Because his hemoglobin level had dropped to 20 per cent of normal, hospitalization and repeated transfusions were necessary. A progress-meal following this episode of intestinal bleeding revealed no evidence of ulcer formation. During the next four years melena occurred at least six times, the longest free interval having been 13 months. Although the patient had never had any abdominal discomfort prior to surgery, from the time of the gastro-enterostomy he experienced occasional episodes of epigastric distress characterized by food and alkali relief; at no time did he have day-to-day discomfort, his epigastric complaints coming on capriciously and sporadically. He was gastroscoped in 1939, and no ulcer was seen. In December of 1940, he consulted Dr. H. L. Bockus for the first time. At that time

physical examination was nonrevealing save for a blood pressure of 160/90. His stools were negative for occult blood. The erythrocyte count was 4.1 million cells per cu. mm., with 11 Gm. of hemoglobins; and the leukocyte count was 7500 cells per cu. mm., with a normal differential. The platelets numbered 127,480 per cu. mm.; bleeding time was 30 seconds; and the Quick prothrombin time was 80 per cent of normal. The gastric analysis revealed no free acid in the first five specimens, bile being present in each extraction; a free acid of 13 units, with a total acid of 28 units, appeared in the sixth extraction. Progress-meal studies revealed no evidence of esophageal varices; an estimated 90 per cent of the barium meal was passing through a well-functioning gastro-enterostomy stoma; no ulcerative lesion of the stomach or duodenum was demonstrated; and the small intestinal loops were considered normal after careful survey. A barium enema study was negative. The Rumpel-Leede test was negative; there was no pathologic urobilinogenuria; and the serum bilirubin was within normal limits. Gastroscopic examination revealed no evidence of bleeding points or ulceration either in the body of the stomach or the well-visualized stoma. The patient was placed on a modified ulcer regimen, and did well for one year, except for occasional mild and transient episodes of epigastric discomfort. On November 30, 1941, however, melena once more recurred, and the patient was hospitalized.

Physical examination on admission revealed no evidences of shock. The blood pressure was 160/85. There was no tachycardia or jaundice, and the liver and spleen were not palpable. A small amount of tarry fecal matter was present in the rectum, but no cherry red blood was seen. Blood studies on admission revealed an erythrocyte count of 5.25 million cells per cu. mm., a hemoglobin of 12.5 Gm., and a leukocyte count of 11,100, with 78 per cent neutrophils. There were 214,000 platelets per cu. mm. No further tarry stools were passed following admission. Patient was treated expectantly, and, December 6, 1941, he was discharged on his previous dietary regimen.

Melena recurred once more in September, 1942, and on the eighth of that month, he was readmitted to the Graduate Hospital. Physical examination at that time revealed a blood pressure of 128/90. The liver and spleen were not palpable, and tarry material was present in the rectal ampulla. His erythrocytes numbered 4.0 million cells per cu. mm., with a hemoglobin of 12.5 Gm. The total leukocyte and differential counts were within limits of normal. There were 168,180 platelets per cu. mm.; and the prothrombin time was 95 per cent of normal. He was treated with hourly feedings, and, September 14, 1942, he was discharged.

He was followed regularly and had no recurrences of his melena until September, 1943, when, while in another part of the country, he suddenly developed another episode of bleeding, which was associated with hematemesis. Because of the severity of his gastro-intestinal hemorrhage he was hospitalized, and on seven occasions transfused. He made a good recovery and was discharged after a month's stay in the hospital. Laboratory studies during the following winter revealed an erythrocyte count of 5.16 million cells per cu. mm., a hemoglobin of 14 Gm.; a leukocyte count and differential within normal range; a platelet count of 304,400 per cu. mm.; prothrombin time of 61 per cent of normal; no retention of dye in 30 minutes with the 2 mg. dose of bromsulphalein; and a gastric acidity of 20 units of free acid and 40 units of total acid. Once more a progress-meal study revealed no evidence of esophageal varices or upper gastro-intestinal tract ulceration.

On March 21, 1944, the patient developed an episode of mild postprandial discomfort localized in the epigastrium, and accompanied by borborygmi. Several hours later he had a passage of liquid fecal material of tarry nature. He became weak and felt chilly, but syncope did not occur. That night he was admitted to the Graduate Hospital for the third time. On examination, the patient was apprehensive, and his skin and mucous membranes were somewhat pale. The blood pressure was 150/90. The abdomen revealed no abnormalities. The red cell count was 4.24 millions per cu. mm., with a hemoglobin of 12 Gm. During the three days following hospitalization melena continued, and despite

repeated transfusions of whole blood and plasma the blood pressure fell to 82/60; the erythrocyte count decreasing to 3.12 million cells per cu. mm., with a hemoglobin of 49 per cent, and a hematocrit of 23 per cent. The patient went into shock late in the afternoon of March 24th, and died several hours later. Autopsy examination was performed one hour after death.

Autopsy.—Examination revealed marked pulmonary edema. Save for an extreme degree of paleness the liver and spleen showed no abnormalities. The esophagus was normal throughout, and no varices were present. The stomach was normal in size and

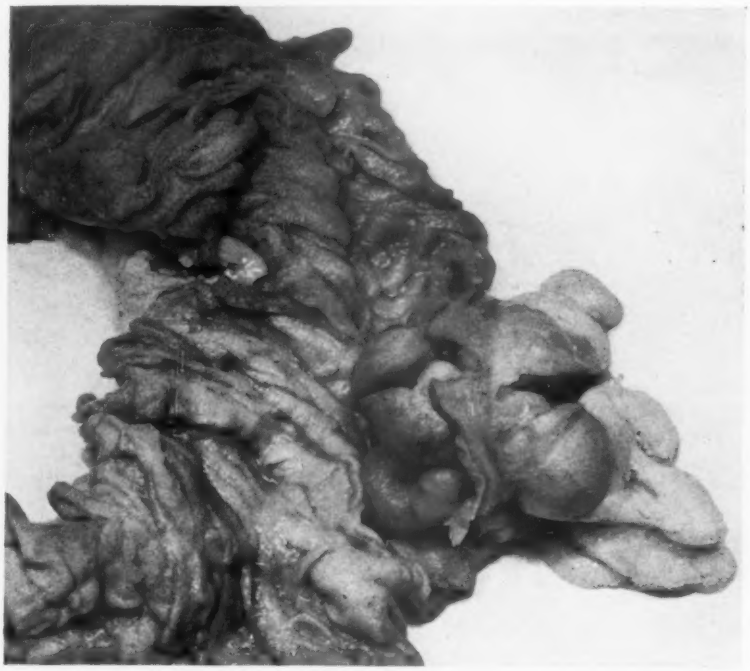

FIG. 1.—Photograph of the gross specimen showing both the submucosal and the subserosal portions of the leiomyoma. Sections have been taken for microscopic study, and the head of the pin used to hold the specimen together should not be mistaken for a part of the lesion.

shape and contained small amounts of bile-stained material; the mucosa showed no injection of erosion, and careful search revealed no scars or ulcerations. A small polypus, 2 to 3 mm. in length, was found along the greater curvature in the pyloric portion of the stomach. The gastro-enterostomy stoma was patent and easily admitted a thumb; no tumefaction or ulceration was found in or about the stoma. The duodenum showed no abnormalities, and the distal and proximal loops of the enterostomy were entirely negative. No blood was present in the stomach, duodenum, or distal or proximal jejunal loops.

Eight inches distal to the enterostomy stoma, in the wall of the distal jejunum, was a firm, somewhat nodulated tumor mass. It was the size of a walnut and was composed of pale, firm pinkish tissue. One-half of this lesion extended submucosally into the lumen of the jejunum, the remainder of the tumor mass presenting subserosally between the layers of the mesentery. The mucosal surface of the tumor was smooth and glistening, and no prominent vessels or bleeding points were to be found on careful inspection. The tumor showed no evidence of ulceration or necrosis. Several centimeters distal to the lesion bright red blood was encountered in the lumen of the jejunum. A short distance

further the material within the lumen became tarry, and the remainder of the small bowel and the entire large bowel was filled with blackish semiliquid fecal material. With the exception of the tumor mass in the upper jejunum no other lesions could be found in the entire gastro-intestinal tract which could explain the melena.

Histologic examination of the tumor tissue revealed the mass to be made up of interlacing bundles and whorls of smooth muscle. The nuclei were vesicular and spindle-shaped; no mitotic figures were seen. Sections stained for connective tissue by Mallory's

FIG. 2

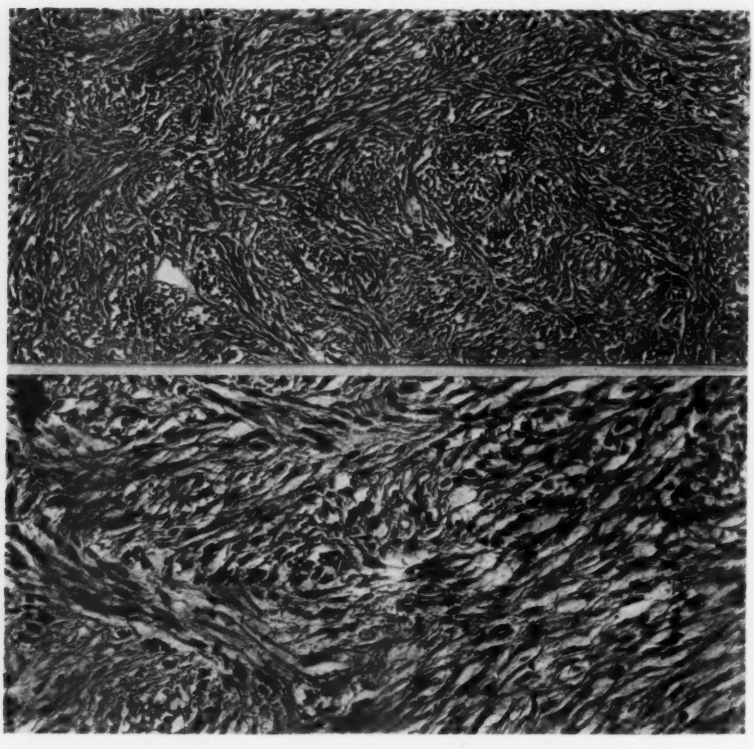

FIG. 3

FIG. 2.—Photomicrograph of the tumor showing the interlacing bundles of smooth muscle in longitudinal section and in cross-section. (Hematoxylin and eosin ×150.)
FIG. 3.—A higher-powered view of a portion of the section seen in Figure 2. The spindle-shaped nuclei are prominent. (Hematoxylin and eosin ×330.)

method revealed only a moderate amount of fibrous supportive stroma. *Pathologic Diagnosis:* Leiomyoma of the jejunum.

DISCUSSION.—This case represents an instance of repeated episodes of melena over the course of a considerable number of years, and a fatal termination from bleeding into the gastro-intestinal tract in a patient who had a benign tumor of the jejunum. It is of interest that ulcer disease, though suspected, had never been demonstrated conclusively, and that a gastro-enterostomy had been injudiciously performed. In all likelihood, had the presence of

a tumor of the small bowel been strongly considered and appropriate surgical exploration advocated, the patient might not have died.

This case emphasizes the fact that the presence of small intestinal neoplasms is much too infrequently suspected. The diagnosis of tumors of the small bowel, both benign and malignant, rests upon a high index of suspicion. The possibility of a neoplasm of the small intestine should be considered in any patient who has repeated episodes of melena in the absence of any demonstrable lesion in the upper gastro-intestinal tract or colon, and in any patient with repeated episodes of partial or complete obstruction in the small bowel. In such instances, despite the absence of roentgenologic demonstration of the lesion, celiotomy is indicated. Since the ratio of benign to malignant tumors is much greater in the small intestine than in other parts of the gastro-intestinal tract, surgery for small bowel tumors should, on the whole, afford a better ultimate result than can be expected for tumors of the esophagus, stomach, or colon.

SUMMARY

1. The incidence, pathologic characteristics, and clinical features of leiomyoma of the small intestines are reviewed.

2. A case of a patient with a leiomyoma of the jejunum who had 20 known episodes of melena over a 14-year period, with a fatal hemorrhage, is reported.

3. The necessity for a high index of suspicion for tumors of the small intestine is pointed out.

We wish to thank Dr. H. L. Bockus for permission to report this case.

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RETROGRADE JEJUNOGASTRIC INTUSSUSCEPTION THROUGH A SUBTOTAL GASTRECTOMY STOMA

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IN 1935, Ducey and McNamara[1] reported a case of retrograde jejunogastric intussusception through a gastro-enterostomy stoma. In a brief survey of the literature the authors found 36 instances of this rather unusual sequela of surgery for relief of peptic ulcer.

The recently encountered case of retrograde jejunogastric intussusception, which forms the basis of this report, was similar in all respects to the one previously described by these authors, with the exception that in this case intussusception occurred through a partial gastrectomy stoma, in the earlier case through a gastro-enterostomy stoma. This fact is of special interest because in recent years gastrectomy has replaced gastro-enterostomy almost universally as the operation of choice for relief of ulcer or cancer. It is believed that this is the first case recorded in which jejunogastric intussusception occurred through a partial gastrectomy stoma.

Case Report.—A. L.; white, male, age 50, gave a history of chancre 20 years ago. He had had inadequate antiluetic treatment, and tabes dorsalis had developed. He complained of "stomach trouble" for many years, and five years prior to the present admission a gastro-enterostomy had been performed for relief of peptic ulcer.

On July 19, 1943, the patient was admitted to the hospital complaining of pain in the upper abdomen, especially severe before meals, and vomiting of "coffee ground" material. Occult blood was detected in the stools. The abdomen was tender. The clinical diagnosis was recurrent ulcer, probably in the gastro-enterostomy stoma, and operation was advised. The patient showed the ataxia of tabes dorsalis. Serologic tests of the spinal fluid were positive. The Wassermann test of the blood was negative.

At operation, September 9, 1943, two large marginal ulcers of the gastro-enterostomy stoma were found. The old anastomosis was excised and a subtotal gastrectomy was performed. The patient made an uneventful recovery and was discharged.

On November 17, 1943, the patient was readmitted, complaining of vomiting and pain in the upper abdomen. The pain was first experienced two weeks before admission (just one week after previous discharge). He had vomited persistently for the last four days. At the time of admission the patient was extremely dehydrated and semicomatose. The vomitus became fecal in type.

The heart and lungs were negative. The abdomen showed an old right upper paramedian scar and a recent but well healed upper midline incision. There was a fullness in the upper abdomen, indefinite in outline and apparently not the liver. The lower abdomen was flat. The patient rapidly lapsed into coma and expired. A tentative diagnosis of intestinal obstruction was made, but immediate surgery was deemed inadvisable due to the patient's extremely grave condition.

Autopsy.—On opening the peritoneal cavity many old fibrous adhesions were noted. There was massive dilatation of the stomach, which measured 50 cm. in length. The lower segment of the stomach had been resected. A retrograde jejunogastric intussusception of the efferent portion of the jejunum had occurred through the gastrectomy stoma.

There was marked dilatation of the afferent loop of the jejunum. The small intestine below the intussusception was collapsed.

On section of the stomach, it was noted that the intussuscepted portion of the jejunum formed a stovepipe-like sleeve, so that there was a double layer of intestine in the stomach. The length of the sausage-like mass in the stomach measured 25 cm., when stretched out it measured in excess of 50 cm. The greater part of the length of the jejunum found in the stomach was partially digested and gangrenous (Fig. 1).

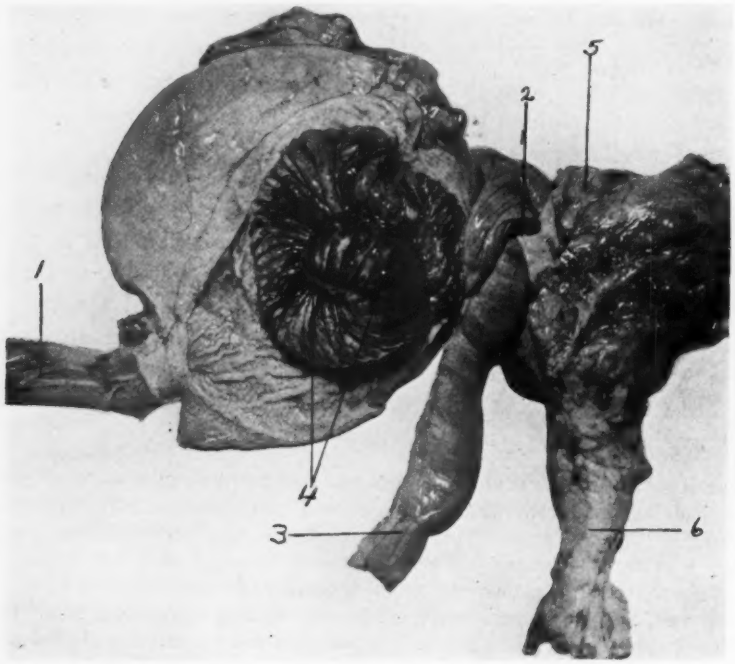

FIG. 1.—Necropsy specimen, posterior view. 1. Esophagus; 2. site of stoma; 3. efferent loop of jejunum; 4. telescoped loop of jejunum filling stomach; 5. blind end of duodenum; 6. pancreas.

There were many adhesions in the area of the stomach and around the blind end of the duodenum. The portion of the small intestine below the intussusception and the large intestine were grossly negative.

Anatomic Diagnosis: Retrograde jejunogastric intussusception through an old partial gastrectomy stoma.

DISCUSSION.—Ducey and McNamara (1937) found 36 cases of jejunogastric intussusception, and added a case of their own. Schackman (1940) notes additional cases by Bonomi (1937), Greenwood (1937) and Otero (1938). Schackman states that if a gastro-enterostomy has both an afferent and an efferent jejunal loop, three types of jejunogastric intussusception may occur: Type I—The afferent loop may intussuscept through into the stomach. Type II—The efferent loop may undergo retrograde intussusception and either stop short of, or pass through, the gastro-enterostomy stoma. Type III—Both afferent and efferent loops together may intussuscept through into the stomach.

Schackman reports a case of Type III in which a preoperative diagnosis of

jejunogastric intussusception within a short time after onset of symptoms, and patient came to operation 15 hours later. The intussusception involving about 3.5 feet of red, congested jejunum was reduced. The gastro-enterostomy stoma was seen and appeared normal apart from a hemorrhagic area 0.5 x 0.5 inches, due to extravasated blood following mechanical congestion on the anterior surface of the anastomosis. No effort was made to anchor the jejunum. The patient made an uneventful recovery, and later by gastroscopy the gastro-enterostomy was demonstrated to function well.

Schackman stresses the necessity for early diagnosis leading to immediate surgery in these cases. From his study he finds that in Types II and III there is a 50 per cent mortality if operation is delayed more than 48 hours after onset of symptoms. Schackman summarizes: "The condition should be considered if ever a patient has abdominal pain and vomiting, with or without hematemesis, coming on at any time after a gastro-enterostomy."

Chamberlin (1940) divides into two clinical groups the reported cases of retrograde intussusception of the jejunum into the stomach (a sequel following gastro-enterostomy) as follows:

"In one group the patients have a brief illness evidenced by epigastric pain and vomiting first of food, then of bile and finally blood. An epigastric tumor may be palpated above and to the left of the umbilicus. Visible peristalsis and upper abdominal rigidity are often present. The usual preoperative diagnoses have been high intestinal obstruction, a ruptured viscus, or an acute surgical abdomen. In this group the prognosis is grave and surgical intervention should be immediate.

The other group of patients is composed of those who maintain a state of chronic invalidism following a gastro-enterostomy for peptic ulcer. The characteristic symptoms beginning at any time from five days to 14, or more, years after operation are epigastric pain, nausea and vomiting which occur at irregular intervals and subside spontaneously. The author adds that in these patients, as in the case of chronic recurrent jejunogastric intussusception through a gastro-enterostomy stoma which he reports, radiographic examination aids in establishing the diagnosis. In this unusual case the intussusception demonstrated repeatedly by fluoroscopic methods was not in evidence when celiotomy was performed about ten days later. The author states that the evidence is conclusive that the patient had a retrograde intussusception of the jejunum which spontaneously reduced itself. The clinical history suggests that this may have occurred many times before the lesion was found, and the history of occasional vomiting attacks subsequent to the operation suggests that it continues to occur.

The case which forms the basis of this report differs from the similar cases in the literature in that the intussusception occurred through a partial gastrectomy stoma rather than through a gastro-enterostomy stoma. It is also interesting that the intussusception occurred so soon after gastrectomy. The operation was performed September 19, 1943 and the first symptoms occurred about six weeks later. Bettman and Baldwin in their résumé noted that the

accident had occurred as early as one year and as late as 16 years after gastro-enterostomy. Due to the delay (two weeks) which intervened between the onset of the initial symptoms (pain and vomiting), and on return of the patient to the hospital the patient was almost moribund and was beyond the aid of surgery when seen. This stresses the importance of early diagnosis and immediate surgery in these cases.

SUMMARY

1. A case is presented in which retrograde intussusception of the jejunum occurred through a gastrectomy stoma.

2. It is important that the possibility of retrograde intussusception of the jejunum through the stoma be considered whenever suggestive symptoms, such as severe pain and bloody vomitus occur in a patient who has been subjected to gastro-enterostomy or subtotal gastrectomy.

3. An early diagnosis is important because immediate surgery constitutes the only hope, except in the chronic type as described by Chamberlin.

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THE INFLUENCE OF ETHER, MORPHINE AND NEMBUTAL ON MORTALITY IN EXPERIMENTAL BURNS*

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THE PRESENT COMMUNICATION deals with experiments showing that the early mortality following severe thermal injury is profoundly influenced by the type of sedation and anesthesia used. In the first paper of this series[1] the combination of nembutal and morphine used produced a good anesthesia during the injury itself, as well as a fairly prolonged sedation afterwards. Following the publication of this data, Dr. Alfred Blalock wrote that he had repeated these experiments and had observed a much lower mortality; indeed, only two deaths occurred under 24 hours in a series of 12 experiments in which a thermal stimulus of 85° to 90° centigrade for 5 to 15 seconds, up to the axilla, was employed. With a similar degree of injury, our mortality was 100 per cent. The fact that he used a smaller dose of morphine without nembutal plus a short ether anesthesia during the burn stimulus suggested that the pronounced difference in mortality might perhaps be due to the type of anesthesia used. In order to study this supposition, a series of experiments were carried out in which a somewhat more severe burn stimulus (immersion up to the axilla at 100° centigrade for 10 seconds) was employed in a series of ten experiments each; various doses of morphine in combination with nembutal or ether were used in each group.

Experimental Findings.—Table I records the essential findings, which indicate clearly the deleterious effect of morphine and nembutal, particularly the former, on the 24-hour mortality.

TABLE I

INFLUENCE OF ETHER, NEMBUTAL AND MORPHINE ON 24-HOUR MORTALITY

No. of Experiments	Agent Used and Dose: Numbutal (i.v.) mg./Kg.	Agent Used and Dose: Morphine* mg./Kg.	Ether during Burn	24-Hour Mortality
10	30	6–10	0	100%
10	30	0	0	50%
10	0	6–10	yes	80%
10	0	3	yes	20%
10	0	0	yes	10%

* These doses, because the dog is much less susceptible than men, are well within therapeutic range.

Hemoconcentration curves were obtained in these experiments, but only those in the three groups given ether are of significance. There was little difference in the two groups receiving both morphine and ether. However,

* Aided by a grant from the Commonwealth Fund.

the group anesthetized with ether, but without morphine, showed a higher peak both in the nine survivals and in the one fatality. From this, it may be inferred that morphine has little influence on the hemoconcentration in burns; if anything, it tends to decrease it. Its deleterious influence, therefore, must be connected not with the physical changes in the blood produced by the burn, but rather with a toxic effect on respiration or on some other vital function.

COMMENT.—The deleterious effect of morphine on the mortality in experimental burns seems quite clear from the present findings. When ether was used during the burn stimulus, the mortality was lowest when no morphine was employed, but increased to 80 per cent when the dose of morphine was 6 to 10 mg. per kilogram. The deleterious effect of nembutal with morphine is shown by the fact that a 100 per cent mortality followed this combination of agents. The inference that nembutal alone is deleterious because it produced a mortality of 50 per cent must be qualified in that the dose employed did not achieve complete anesthesia so that the relatively high mortality might have been due in part to an incomplete central suppression of the afferent impulses during the stimulus. The wide differences in mortality herein observed show how important it is to evaluate the effect of the anesthesia in experimental burns before drawing inferences from the value of various therapeutic procedures. In shock due to other injury contrasting findings have been reported. Thus, experiments[2] with hemorrhagic shock have shown no difference in mortality between those given morphine as compared with controls. Another study,[3] together with an analysis of preceding work, showed that shock from intestinal manipulation is delayed with barbiturate as compared with ether anesthesia, but that in shock from hemorrhage there was no significant difference.

Practical inferences may be drawn from the present study in view of the almost universal use of large doses of morphine in the treatment of human burns. While no one will question the beneficial effect of morphine in the presence of really severe pain, its cautious use must be emphasized when such pain does not exist. The present author has observed many severe human burns in which pain was completely absent at the time the patient was first seen. Indeed, the sensorium was often dulled in the severe cases. It is quite probable that by the time the burned patient is able to receive medical care, pain has disappeared almost entirely except for the memory of the intense pain at the very moment of the injury. Under such conditions, large doses of morphine should certainly not be used, inasmuch as it may lead to harmful effects, perhaps even increasing the mortality in spite of the use of other beneficial therapy.

CONCLUSIONS

Morphine increases the 24-hour mortality (up to 100 per cent) in severe experimental burns, particularly when given in large doses and with nembutal. Practically no 24-hour mortality occurred when ether alone was employed.

It is inferred that large doses of morphine, when used in the absence of pain, may increase the early mortality in severe human burns.

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CLOSURE OF DEFECTS OF LIPS WITH COMPOSITE VERMILION BORDER-LINED FLAPS*

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DEFECTS OF THE LIPS large enough to prevent direct closure can be closed by transplantation of flaps either from the immediate neighborhood or from some distant parts. If possible, composite vermilion border-lined flaps shifted or rotated from the immediate neighborhood should be chosen. Flaps from distant parts have the disadvantage of requiring considerable amount of time for their transplantation, difference in skin color and texture, and loss of function.

CLOSURE OF VERTICAL LIP DEFECTS NOT LARGER THAN HALF THE WIDTH OF THE LIP

Estlander's Operation: The principle of the method consists in covering the defect by formation and rotation of a full-thickness flap from the opposing lip. The flap is pedicled at one side of the vermilion border, which contains the coronary artery. Estlander's original operation was devised for closure of triangular defects of the lower lip near the corner of the mouth. This operation has been modified, since then, in many ways (Abbé, Buck, Brown, Padgett, Cannon). Some of the different ways in which Estlander's principle can be employed are outlined in Figures 1, 2, 3, 4 and 9. In those defects in which the corner of the mouth is included, the pedicle of the flap forms the new corner of the mouth. This usually causes some vertical shortness and, consequently, prevents the patient from opening the mouth fully, Figures 1, 2, 3 and 9. To overcome the handicap, I recommend a procedure to be performed three weeks after the first operation, as outlined in Figure 2. The principle is based on the switching of triangular flaps like in Z operations. Thus, not only the oral orifice is widened, but a more natural corner of the mouth is achieved, Figures 2 and 9.

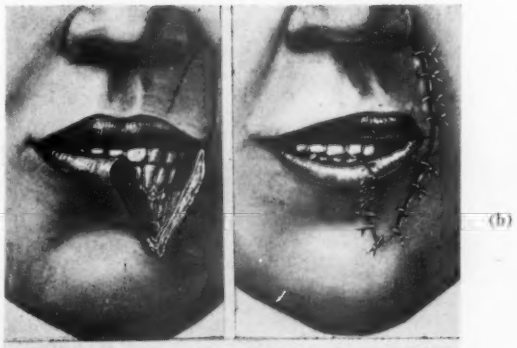
CLOSURE OF LARGE HORIZONTAL DEFECTS OF UPPER OR LOWER LIP (EXCLUDING THE CHIN)

These defects may involve partial or full-length of the lips. A great number of procedures are described in the literature which recommend the use of full-thickness cheek flaps. Some of them have never been practiced and some of them give such poor cosmetic and functional results that they should be abandoned, both from surgical practice and textbooks.

Brun's operation is still highly recommended in some of the textbooks. This method was tried by the author, but was far from the result which the classic illustrations would make one believe. But, there are a few excellent procedures available which make use of flaps from the immediate

* Presented before the Philadelphia Academy of Surgery, December 1, 1943.

FIG. 1



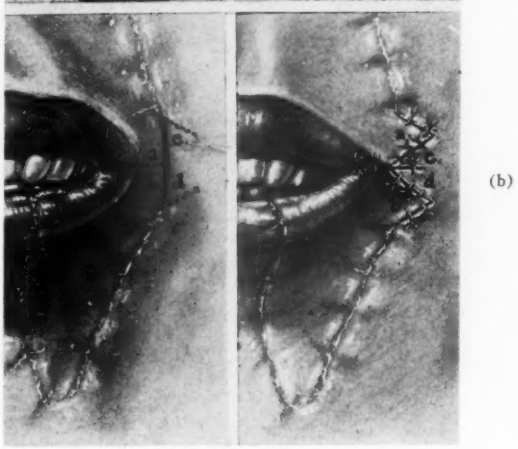


FIG. 2

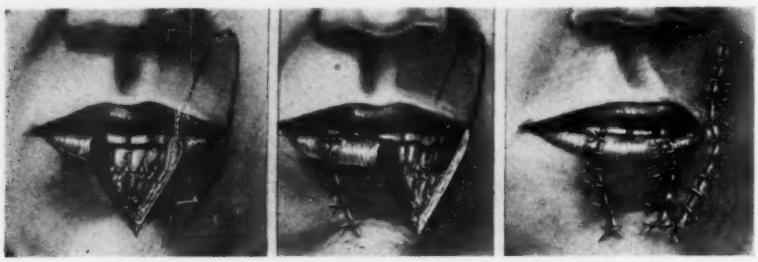
FIG. 1.—(a) Triangular defect of lower lip not larger than one-half the width of the lip. The defect includes the lower border of the left corner of the mouth. To close the defect, a vermilion border-lined flap is to be rotated from the upper lip and the naso-labial region The pedicle of the flap containing the coronary artery is to replace the corner of the mouth. The flap should be made one-half as wide as the defect in order to shorten upper and lower lip proportionately. (b) The flap is rotated into the defect. The secondary defect is closed by suturing the wound edges together.

FIG. 2.—(a) Reconstruction of corner of mouth in those cases in which the pedicle of the flap (see Figure 1) forms the new corner of the mouth. The vertical shortness is overcome by switching triangular flaps. Flap (a) is exchanged with flap (c); flap (b) with flap (d). Thus not only the oral orifice is widened, but a more natural corner of the mouth achieved.

neighborhood consisting of skin and subcutaneous tissue only, and are recommended whenever they are possible. I refer to the ingenious methods of F. Smith, Pierce, O'Connor, and Owens.

CLOSURE OF DEFECTS OF LOWER LIP AND CHIN OF NOT LARGER THAN THREE-QUARTERS THE WIDTH OF THE LIP

For closure of these defects, utilization of composite flaps from the immediate neighborhood is still possible.



(a) (b) (c)

FIG. 3.—(a) Triangular defect in the middle portion of the lower lip. In order to make the method of Figure 1 possible, the defect must be transferred laterally. This is done by closure of the center defect with a square flap. The outlines of this flap as well as the flap of the upper lip are illustrated. (b) The square flap for closure of the center defect is rotated into the defect. This opens up a similar defect in the lateral portion of the lip. (c) The flap from upper lip is rotated in the lateral defect. The secondary defect of the nasolabial region is closed.

Burow's Method: To use this method, the defect must be triangular-shaped. It is closed by shifting tissue from the immediate neighborhood into the defect after sacrificing two triangles of tissue in the nasolabial region.

The excision of lip and chin should be rather heart-shaped, than wedge-shaped (Diffenbach). This results later in a more normal looking profile with a dimple in the center of the chin.

The triangles of tissue to be excised from the nasolabial region should consist of skin and muscle only. The base of the triangle is in line with the vermilion border and equals in length one-half the width of the defect. The mucous membrane floor of the triangular defect is incised as outlined in Figure 5. If turned outward, it will lengthen the vermilion border. The purpose for shaping the small mucous membrane flaps, as outlined in Figure 5, is twofold: (1) A gradual tapering off of the new vermilion border at the outer angles which are to form the new corner of the mouth; and (2) a more satisfactory adjustment of the mucous membrane flap to the gradually disappearing original vermilion border. As a rule, a small triangle of skin needs to be removed at the corner of the mouth to make room for the tip of the mucous membrane flap (New and Figi). The flaps are now turned outward and sutured in place. The lateral part, however, where the new vermilion border is tapering off, due to thickness of the cheek tissue, may be too broad; it should be thinned somewhat by excision of a wedge of subcutaneous and muscle tissue.

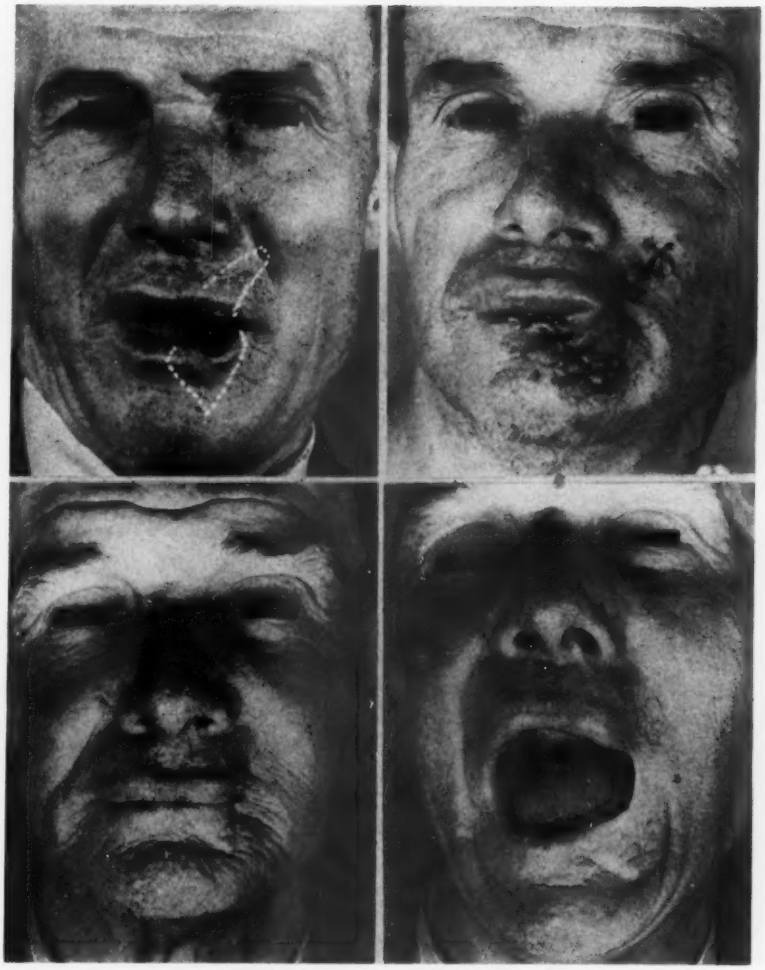
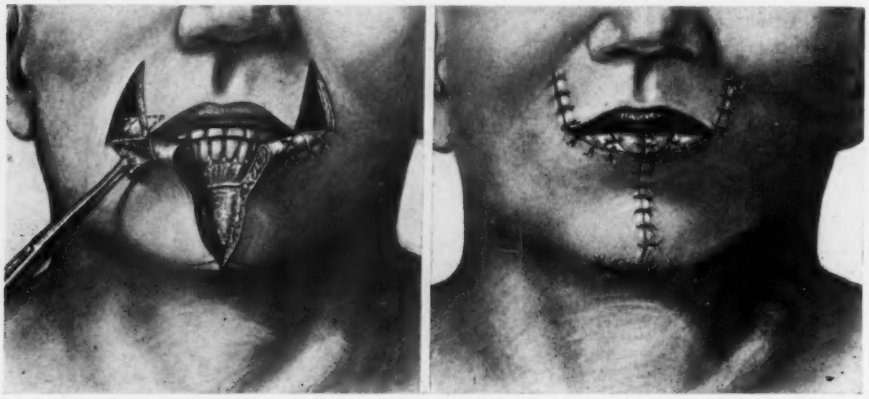


FIG. 4.—(a) Small recurrent cancer of left half of lower lip. Excision at lower lip and flap at upper lip marked out. The width of the flap is only one-half of that of the defect, in order to shorten upper and lower lip proportionately. (b) Ater rotation of the flap; the left corner of the mouth is preserved; the pedicle of the flap crosses the mouth. (c) Three months after separation of the pedicle. (d) Mouth can be opened to almost full extent.

The cheek flaps to be shifted into the defect are mobilized from the mandible from an incision along the lower gingivobuccal sulcus. The dissection should be carried back to the anterior border of the masseter muscle. The mobilized flaps are now pulled forward and anchored in this position



(a) (b)

FIG. 5.—(a) Burow's method of closure of triangular defects of lower lip and chin, of not larger than three-quarters the width of the lip: Closure of the defect by shifting tissue from the immediate neighborhood into the defect after sacrificing two triangles of tissue in the nasolabial region. The excision of the triangles should consist of skin and muscle only. The incision of the mucous membrane floor of the triangular defect is outlined. If turned outward, the mucous membrane flaps lengthen the vermilion border. A small triangle of skin near the corner of the mouth needs to be removed for adjustment of the mucous membrane flap A horizontal incision below the chin may facilitate shifting of the main flaps. (For details, see text.) (b) After closure of primary and secondary defects.

(a) (b) (c)

FIG. 6.—(a) Defect of lower lip and replacement of soft tissue by dense fibrous tissue after radiation of a hemangioma. Patient was operated upon according to the method of Figure 5. (b) Soon after the operation. (c) One year after the operation.

to the gums. Each suture should be placed obliquely so that it advances the flap forward. Then follows closure of the triangles in layers, connection of the lateral edge of the new vermilion border to the upper lip and vertical connection of both flaps in the midline in layers. Some adjustment may be

necessary at the bottom of the incision to avoid pointing of the chin. A drain is inserted in the lower corner of the vertical wound.

Variations: If the defect is more laterally situated this method may be

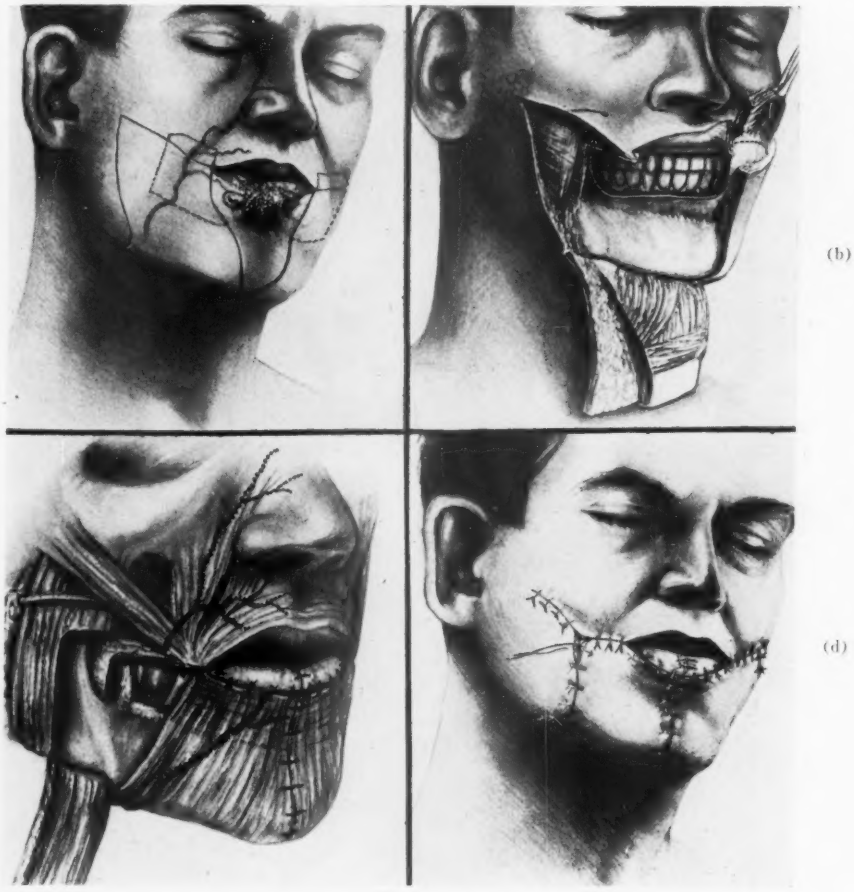


FIG. 7.—(a) Modified Dieffenbach's method for closure of large defects of lower lip and chin: Heart-shaped excision of lower lip and chin is outlined, also the two square flaps which are to cover the defect. Two small flaps at corner of mouth are preserved; the inside incisions for mobilization of the flaps from the mandible and from the anterior border of the masseter muscles are outlined by dotted lines, also the small mucous membrane flaps for formation of the vermilion border. (b) The right flap is mobilized; the small mucous membrane flap is sutured to the outer edges of the main flap; the left mucous membrane flap for formation of the vermilion border is being freed. (c) Closure of the triangular muscle and mucous membrane defect in front of the masseter muscle by mobilization of the mucous membrane as far as possible and transplantation of a flap consisting of the lower anterior half of the masseter muscle. The mobilization of the flap is exaggerated in this drawing for demonstration purposes. (d) The original and secondary defects are closed. (Courtesy, Surg. Gynec. & Obst. 73: 236, 1941.)

carried out unilaterally and be combined on the other side either with Estlander's or—in large defects—with Dieffenbach's method (*vide infra*).

Bernard's Operation: This operation is similar to Burow's, with the exception that the defect is made square, instead of triangular. Martin improved the technic by adding some modifications.

CLOSURE OF DEFECTS OF ENTIRE LOWER LIP AND CHIN

In such large defects, a lined flap from distant parts of the body will be the method of choice in a number of cases, particularly for square, irregularly-shaped defects. If, however, the defect can be made triangular, transplantation

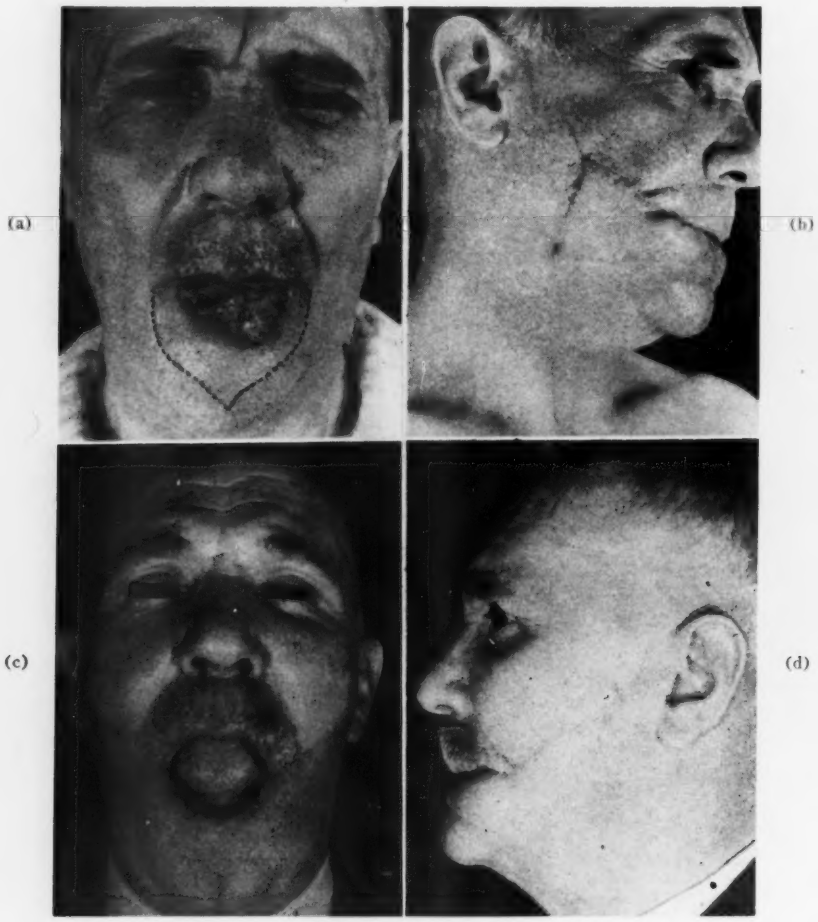


FIG. 8.—(a) Patient with large squamous cell carcinoma of lower lip—no evidence of metastasis. Line of heart-shaped excision outlined. Operation according to the method of Figure 7. (b) Same patient five days after operation. (c) Same patient 13 months after operation. (d) Same patient 13 months after operation. (Courtesy, Surg. Gynec. & Obst. 73: 236, 1941.)

of composite flaps from the immediate neighborhood may be possible. I recommend the modified Dieffenbach operation for such a case. This method has been frequently accused of being mutilating and extensive. It will not be denied that the operation is extensive, but—correctly performed—it is not mutilating. I have endeavored to improve the technic by adding a few more modifications. From the cosmetic functional and economic standpoint, it is by far superior to any existent flap transplantation. The advantages are: Exci-

sion of the diseased part and closure of the defect in one sitting, thus shortening hospitalization; and replacement of lost structures by similar structures, thus restoring original function and appearance. This operation can be performed unilaterally or bilaterally; it can be combined with other operations such as Estlander's or Burow's; it can also be combined with resection of

FIG. 9.—(a) Patient with squamous cell cancer inside the mouth near right corner. Triangular excision including upper half of corner of mouth and parts of the adjacent cheeks is outlined. Triangular vermilion-bordered flap at lower lip is outlined. (b) Before the flap was rotated into the defect, the latter was made smaller by closure of the lateral corner. The pedicle of the flap forms the new corner of the mouth. (c) Four weeks after operation. (d) The vertical shortness at the right side of mouth was corrected according to the method of Figure 2.

bone. I have described the technic in a previous publication. Figures 7 and 8 depict technic and result. Lymph-glands, if necessary, should be resected in a second stage.

CLOSURE OF DEFECTS OF THE CORNER OF THE MOUTH AND PARTS OF THE ADJACENT CHEEK

If the defect includes only one-half of the corner of the mouth (the corner part of either the upper or lower lip), and parts of the adjacent cheek, and

if the defect can be made triangular, Estlander's method is the operation of choice. The patient in Figure 9 is a typical example. Before rotating the vermilion-bordered triangular flap into the defect, the latter is made smaller by starting with closure of the lateral corner of the triangle until the corner of the mouth, *i.e.*, the remaining half of it, is reached. Now, the triangular flap is formed from the sound lip opposite to the defect and rotated into the defect as described above. In a second stage, the pedicle of the flap

(a) (b) (c)

FIG. 10.—(a) Patient with long standing keratosis cancer in right corner of mouth. Diamond-shaped excision outlined. (b) After closure of the defect by starting with closure of the corners. (c) Same patient six months after first operation and five months after correction of shortness of right side of mouth according to the method of Figure 2.

is severed and adjusted as shown in Figure 2. This will widen the oral orifice and achieve a more natural corner of the mouth.

If the upper and lower part of the commissure, *i.e.*, the entire angle of the mouth and adjacent parts of the cheek, must be excised, and the resulting defect is of such size that closure can be achieved by simple skin sliding, the defect should be given a shape, as outlined in Figure 10: An upper and a lower triangle with a common base, resulting in a diamond-shaped defect. The latter is closed by starting with closure of the corners, Fig. 10. If this procedure results in a microstoma on the operated side, the deformity can be improved according to the method of Figure 2.

SUMMARY

Various operations to close defects of lips alone, or lips, chin and cheek, with composite vermilion border-lined flaps from the neighborhood, have been described. Only those methods have been selected which have proven to be of practical value.

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DUPUYTREN'S CONTRACTURE: FIBROMA OF THE PALMAR FASCIA

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THE PROGRESSIVE unilateral or bilateral contracture of the fingers of the ulnar side of the hand, which we know as Dupuytren's contracture, had been described prior to 1832, when the great French surgeon whose name it bears called attention to the fact that the actual shortening occurred in the palmar fascia and did not involve the tendons. This observation has since been universally confirmed and, on this basis, successful surgical treatment has been possible. Despite numerous subsequent attempts to explain the nature of the change in the palmar fascia, no satisfactory theory of etiology has as yet been advanced. It is the purpose of this paper to show that Dupuytren's contracture is due, in a series of cases, to a neoplasm—a cellular fibroma of the palmar fascia.

THEORIES OF ETIOLOGY

Some of the many theories of the nature of Dupuytren's contracture may be mentioned, though many have not received adequate support to warrant discussion here. Abbott,[1] quoting from many sources, mentions the possible contributions of a familial trait; an ulnar nerve lesion; endocrine disturbances; and dental and tonsillar sepsis. There can be no controversy over the fact, repeatedly observed by many writers, that several persons in the same family and in succeeding generations may suffer from the contracture, but this interesting fact actually casts no light on the cause or nature of the disease. The suggestion that there may be a lesion of the ulnar nerve seems to grow out of the predilection of the contracture for the ulnar side of the hand, though rarely, if ever, can such a lesion be demonstrated. The frequent simultaneous occurrence of Dupuytren's contracture and arthritis, together with the difficulty of adequately explaining the cause of either, has led to the suggestion that focal infection, thought by many to be implicated in arthritis, might play a rôle in the contracture as well.

Kanavel, Koch, and Mason[2] have gathered from the literature five additional suggested causes. These are trauma (Dupuytren himself thought the disease resulted from repeated trauma); local inflammation; lead poisoning; loss of fat with advancing age; and embryonic malformation. They discuss the rôles of trauma, "a constitutional vice like gout or rheumatism," and heredity. In eight out of 29 patients they elicited a definite family history of Dupuytren's contracture. They found that their patients had

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about the same incidence of gout and rheumatism as could be found in a group of comparable ages, not suffering from contracture. Sixteen of their patients gave histories of trauma to the palm to which they attributed their disease. The authors point out that the histories are all unconvincing. They ultimately conclude that the etiology of the contracture is unknown.

Gill,[3] and Davis and Finesilver[4] point out the unlikelihood of trauma as an etiologic agent because (a) the disease usually has a late onset after the completion of the working years, in which trauma to the palms is most likely to be sustained; (b) there are relatively few cases among laborers and many among "white-collar workers" (Kanavel, Koch, and Mason reported 321 cases of which 175 occurred in nonlaborers, while 146 were in laborers); (c) trauma is usually unilateral, while the contracture is often bilateral (313 cases out of 648 reported by Kanavel, Koch, and Mason); and (d) trauma to the palm is much more common than Dupuytren's contracture.

Brooks[5] has reported a case in which a unilateral Dupuytren's contracture was associated with an aneurysm of the axillary artery, and which almost entirely disappeared following proximal ligation and distal reconstructive endo-aneurysmorrhaphy of the aneurysm.[6] In this connection, the author recalled as examples of fibrosis associated with impairment of blood supply the contracture of Volkmann, and the scarring of the tissues of the leg distal to varicose veins.

The suggestion that the contracture is due to a neoplasm is rare in the literature. Horak,[7] histologically, found no actual inflammation, and concluded that the process lay on the borderline between inflammation and new growth. McWilliams[8] stated that the process was a "chronic hyperplastic inflammation of the palmar fascia and adjacent connective and fatty tissue" involving only certain portions of the tissue at a time and producing the "small tumors felt in the palm."

Ewing,[9] though he states that the etiology of the contracture is undetermined and does not actually say that it is a neoplasm, implies a recognition of its neoplastic character by discussing it in the chapter on fibromata in his book, "Neoplastic Diseases." The issue is somewhat clouded, however, by the unfortunate fact that the condition is classified under tumors of peripheral nerves in the subgroup "elephantiasis," which also includes inflammatory types. He states: "Hyaline changes are not infrequent and the structure then resembles that of keloid. Occasionally, the structure is more cellular and resembles hyaline neurofibroma, with appearance of somewhat numerous, large polyhedral cells of uncertain origin." Unfortunately, the vagueness of these statements makes it difficult to be sure whether Ewing believed the contracture was neoplastic.

In this connection it is of interest that McWilliams,[8] Kanavel, Koch, and Mason,[2] Abbott,[1] Meyerding,[10] and Davis and Finesilver,[4] all emphasize the fact that the first symptom of contracture is a palpable nodule in the palm,

The material for this study comes from 22 hands of 17 patients operated upon for Dupuytren's contracture in the Johns Hopkins Hospital, and from

whom excised tissue was saved for study. Fifteen cases were in males and two cases in females. The contracture was unilateral in 10 cases and bilateral in seven, but one hand of one patient had previously been operated upon elsewhere, and the specimen from one hand of another is no longer available. In 15 patients the history of onset is available and in eight of these a nodule in the palm was the first thing noticed, even before contracture began. Five patients stated that other members of their families suffered from contractures of the fingers. In only one case was there a history of trauma to the palm, while in three this factor was not touched upon in the history.

The histologic picture of the tissue excised is surprisingly uniform. In 17 hands of 14 patients there are areas of rather cellular fibroma interspersed with areas of hyaline-appearing fascia. Among the five cases with bilaterally operated contractures, from both of whose hands tissue is available, tumor is

TABLE I

FINDINGS IN SEVENTEEN CASES OF DUPUYTREN'S CONTRACTURE

Case No.	Unit No.	Sex	Hands Involved	History of Trauma	Family History	Onset with Nodule	Fibroma Found
1	227601	M	1	0	+	0	+
2	195763	M	1	0	0	0	+
3	187206	M	1	0	0	+	+
4	170333	F	1	0	+	+	+
							0
5	135119	M	1	0	0	0	Skin only
6	57522	M	1	?	0	?	+
7	52836	M	2				0
			1 lost	0	+	+	Subcutaneous tissue only
8	44676	M	1	0	0	+	+
9	36027	M	1	?	0	+	+
10	35603	M	1	?	0	?	+
11	25406	M	2				
			1 operated	0	0	0	+
12	146873	F	1	0	0	+	+
						0	+
13	262778	M	2	0	+	0	+
						0	0
14	30531	M	2	0	0	0	+
						0	0
15	61976	M	2	+	0	0	0
	[redacted]					+	+
16	38855	M	2	0	0	+	+
						+	+
17	283453	M	2	0	+	+	+
Totals.....		15 male 2 female	22	1	5	8 cases 10 hands	14 cases 17 hands

present bilaterally in three cases, absent bilaterally in one case, and present unilaterally in one. Of the 17 hands which histologically show fibroma, three failed to do so in the original section, and the neoplasm was revealed only on serial section of the blocks of tissue saved. Serial sections were also made from the blocks of the five hands which failed to reveal fibroma, and one of these proved to consist only of skin and subcutaneous tissue, while another was subcutaneous fat only—indicating that in these cases either the operator or the pathologist missed the palmar fascia. The other three negative blocks

show hyaline-appearing fascia identical with that which is interspersed between the areas of tumor in the remaining cases. Since in each case the pathologist imbedded for sectioning only a representative piece of the tissue removed, and since in three cases mentioned above only hyaline fascia was seen until the blocks were sectioned serially, it is possible or even probable that fibroma was actually present in the negative cases also. These data are recorded in Table I.

HISTOLOGY OF TUMORS

The fibromata in these cases are rather poorly demarcated, fading out into the surrounding fascia. They are composed of small, spindle-shaped cells, with elongated nuclei which contain finely granular chromatin particles. The cytoplasm is scanty and poorly outlined. These cells are imbedded in a matrix of fibrous tissue whose wavy pattern is suggestive of normal fascia or tendon. There are suggestions of whorls, and the bundles of cells run in various directions, some lying in the plane of, and some perpendicular to, the plane of any section. No mitoses are seen, and the cells are all quite alike. Inflammatory cells are so rare as to be almost nonexistent. Photomicrographs of representative cases of these tumors, demonstrating these various characteristics, are seen in Figures 1–3, inclusive, while a higher magnification, to indicate the waviness of the stroma, is seen in Figure 4.

These fibromata are histologically almost identical with the benign fascial fibromata seen elsewhere, especially with desmoid tumors of the abdominal wall. Two of these latter tumors are shown in Figures 5 and 6, for comparison. Figure 7 shows another histologically similar fibroma which arose from the fascia of the popliteal space, and Figure 8 is another such tumor which originated in the plantar fascia of the foot. These latter tumors, while they slowly invade the surrounding structures, do not metastasize. Quite obviously, the benignancy of the fibroma seen in Dupuytren's contracture is confirmed by the failure of the literature to record metastasis in any of the many reported cases.

CONCLUSIONS

No real conclusion as to the etiology of Dupuytren's contracture has previously been reached. In general, various suggestions have been made—trauma; familial trait; focal infection; ulnar nerve lesions; endocrinopathy; local inflammation; embryonal malformation; palmar atrophy with advancing age; and lead poisoning, *etc.* None has been generally accepted, and much of the discussion of etiology has been directed toward proving that these are *not* the causes of the contracture.

While to say that a lesion is a neoplasm is admittedly no explanation of its cause, it at least indicates the general type of abnormality with which one has to deal. The present study of tissue removed from 22 hands of 17 patients with Dupuytren's contracture reveals areas of cellular fibroma in the palmar fascia in 17 hands of 14 patients, while the tissue from two hands does not

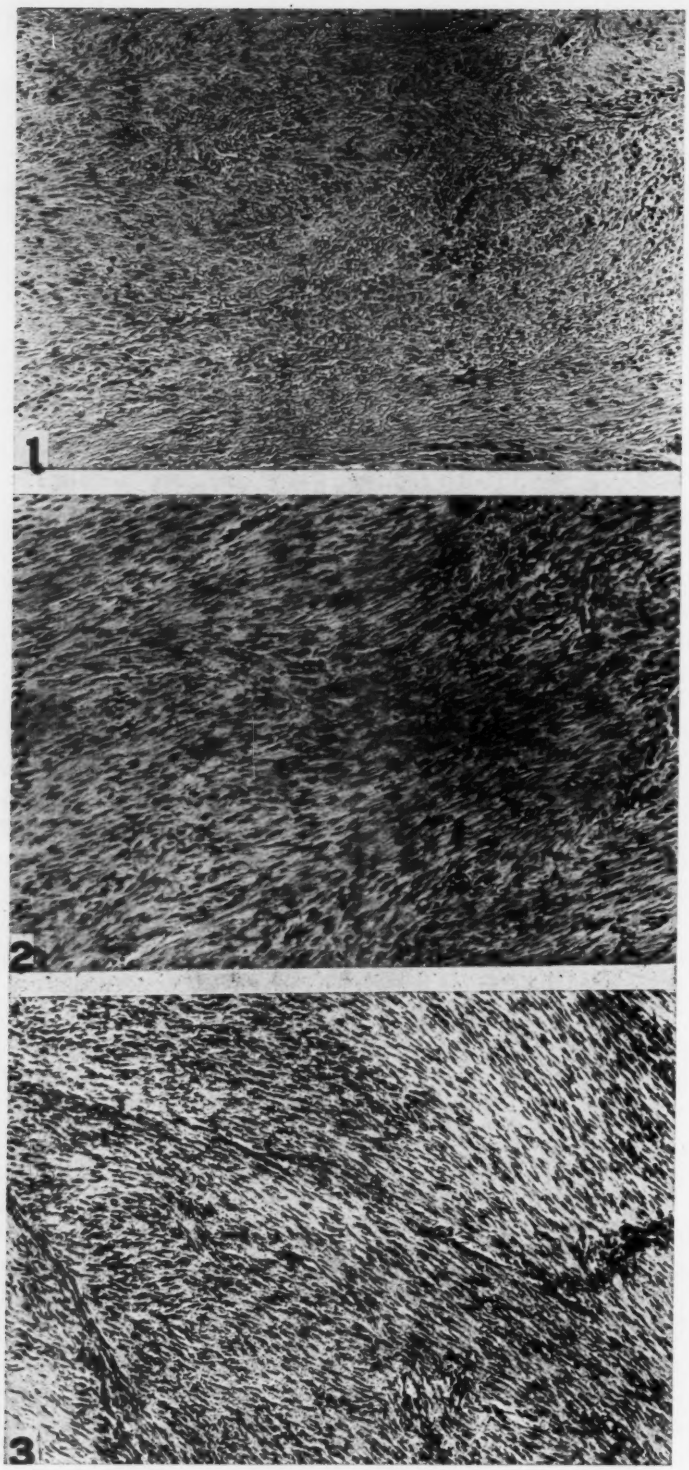
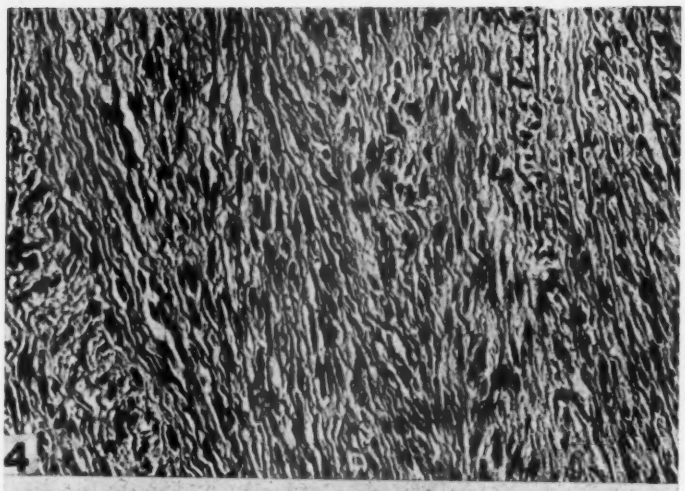
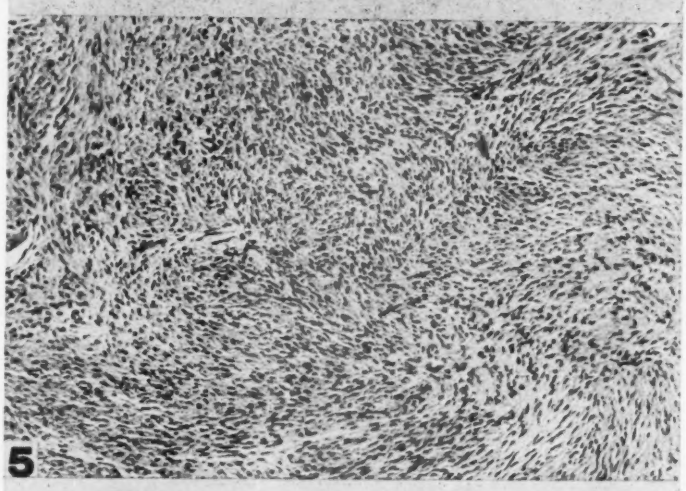


FIG. 1.—Case 1: Fibroma of palmar fascia from Dupuytren's contracture. Tumor is composed of elongated cells in a fibrous matrix. Bundles of fibers and cell nuclei course through tumor in various directions.
FIG. 2.—Case 11: Fibroma of palmar fascia from Dupuytren's contracture.
FIG. 3.—Case 17: Fibroma of palmar fascia from Dupuytren's contracture.





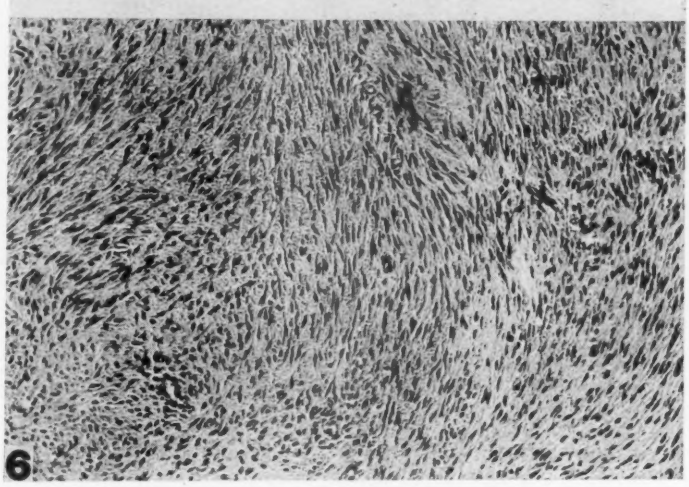


FIG. 4.—High power magnification of fibroma of palmar fascia from Case 11, showing wavy fibrillary pattern of stroma.

FIG. 5.—Fibroma of fascia of abdominal wall (desmoid tumor) from a 25-year-old white male. (Compare with Figures 1-3.)

FIG. 6.—Fibroma of fascia of abdominal wall (desmoid tumor) from a 24-year-old white female. (Compare with Figures 1-3.)

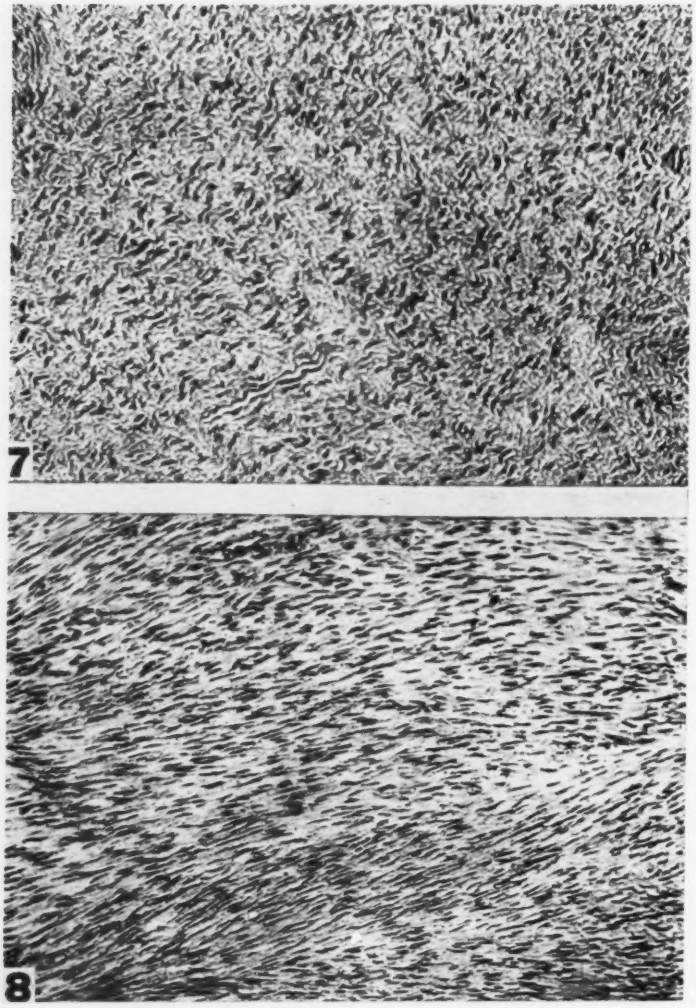


FIG. 7.—Fibroma of fascia of popliteal space from a 23-year-old white female. (Compare with Figures 1-3.)

FIG. 8.—Fibroma arising in plantar fascia of a 21-year-old white female. This tumor had been present since childhood and was 2 cm. in diameter. (Compare with Figures 1-3.)

include the palmar fascia. As has been pointed out, the method employed in preparing the specimens for microscopic examination makes it possible that tumor was present in the palmar fascia of the three remaining hands.

In addition, in eight of the 15 patients in whom a history of onset is available, a palpable nodule in the palm was the first symptom of the disease, even preceding the onset of contraction of the fingers. This is in agreement with the histories, previously quoted by several authors, and seems very significant in the light of the subsequent histologic finding of fibromata.

The predominance of males, 15 of 17 patients, as well as the family history

of Dupuytren's contracture given by five patients, agrees with previously reported data. It would be of interest to see whether other fascial fibromata, including the desmoid tumors, have a tendency to familial occurrence. This point has generally not been mentioned in the recorded cases, and in one large series[11, 12] it was not observed. Among 14 patients whose history touches on this point, only one gave any suggestive history of trauma to the palm.

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OMENTAL CIRCULATION IN MORPHINIZED DOGS SUBJECTED TO GRADED HEMORRHAGE*

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The capillary bed, as an organized, functioning unit, offers the logical site for a study of shock involving a progressive deterioration and an ultimate failure of the peripheral circulation. Recently Root and Mann,[1] and Page and Abell,[2] studied this aspect of the problem by making direct observations on the peripheral circulation in the mesentery of experimentally treated animals. Root and Mann subjected rats to tourniquet shock and reported a general congestion of the capillaries which they concluded was not to be ascribed to histamine. Page and Abell studied the effects of hemorrhage and of venous tourniquets on cats and dogs. They reported an over-all ischemia of the capillary bed resulting from a widespread vasoconstriction.

Unfortunately, in the above investigations, no special attention was given to several important points. One of these deals with the independent reactions of the capillary bed, a feature stressed by those who have made a specialty of the capillary circulation, (Lewis,[3] Krogh,[4] Dale and Richards,[5] and, more recently, Zweifach[6]). A second point is the danger of generalizing from one set of observations without ascertaining the extent to which the vascular bed studied is typical. A third point, which is probably the most important and applies particularly to the observations of Root and Mann, is the necessity of rigid precautionary measures for obviating trauma incidental to handling of a tissue while preparing it for the observations. Krogh,[4] Landis,[7] and others, have emphasized that even slight abnormalities of the surroundings seriously affect the behavior of the capillary vessels. This is especially true for mammalian tissues where not only a minimum of handling, but also anesthesia, temperature and the make-up of the bathing medium play a crucial rôle. The significance of the normal reactivities of the capillary circulation

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in the dog and rat and the means for maintaining them have been presented in detail elsewhere.[8, 13]

It is well established that various types of trauma involving fluid loss are accompanied by a widespread vasoconstriction. Investigators who have examined the peripheral circulation in the cutaneous tissues[9, 10, 11] where little or no handling of the tissue was involved in making the observations, agree on the development of a marked vasoconstriction resulting in complete ischemia of the tissue. Page and Abell[2] claim this to be true also for the intestinal mesentery exteriorized in a specially constructed transparent chamber. In an earlier publication from our laboratory,[12] observations were made simultaneously on the cutaneous vessels of the interdigital web and the visceral vessels of the meso-appendix of rats traumatized by the Noble-Collip drum. It was found that the vasoconstriction affected the cutaneous much earlier than the visceral vessels. Moreover, the ischemia of the skin vessels was so complete as to render visualization of the capillary bed very difficult even during the earlier stages of the shock syndrome. On the other hand, the visceral vessels remained plainly visible throughout the syndrome and the progressive changes in the capillary bed could be readily followed.

An analysis of the structural and functional aspects of the normal peripheral circulation in the frog and mouse has been presented by Zweifach.[13] This has been more recently amplified by a study of the normal visceral capillary circulation in animals which are commonly used for shock studies, *viz.*, the rat and the dog. On the basis of the findings on the meso-appendix of the rat and the omentum of the dog, a number of well-defined criteria have been assembled which make it possible to analyze, more adequately than hitherto, changes which are induced by various experimental procedures.

This paper is restricted to a study of the circulatory changes in the omentum of morphinized dogs induced by a specific type of graded hemorrhage.[14, 15, 17] Hemorrhage as a procedure for inducing shock was selected because it offered a relatively simple and controllable approach to the problem. A study of circulatory collapse induced by acute hemorrhage is being presented in another paper.[16] This study deals more particularly with the effect of inducing hypotension in morphinized dogs and of prolonging the hypotension (by repeated small infusions) until a circulatory collapse occurs which is refractory to the infusion of all the blood withdrawn during the syndrome.

TECHNIC

Preparation of the Omentum.—The dogs were given a subcutaneous injection of morphine sulfate (12 mg./Kg.) and, 30 to 45 minutes later, part of the omentum was carefully withdrawn through a transverse abdominal incision and was spread on a specially constructed moist chamber on the stage of a microscope. This method, the details of which are given in a previous paper, maintains the exposed omentum with a normal circulation for six to eight hours. The essential feature is maintenance of the entire

exposed portion at body temperature and moistened with a constant drip of warm gelatin-Ringer's solution.* The observations were made on selected vessels throughout the course of an experiment, under magnifications of 80 to 345 times.

Bleeding.—The method of bringing the dogs into a hypotensive state, from which they no longer can be restored by the infusion of the blood withdrawn, is essentially that recommended by Wiggers and Werle.[17] The dogs were routinely bled at 10- to 15-minute intervals by the successive removal of blood in amounts of 2.0, 1.0, 0.5 and 0.25 percentages of the body weight, or until the blood pressure reached hypotensive levels below 70 Mm. The pressure was taken from the carotid, and a continuous record made on a kymograph drum throughout the experiment. The dogs were first brought to, and kept in, moderate hypotension, within the range of 50 to 70 Mm. Hg., for varying lengths of time, and then were brought into drastic hypotension and kept there for another length of time. The blood withdrawn was preserved with 0.2 per cent sodium citrate for infusion purposes.

The majority of the dogs (46 out of 65) could not be kept at the drastic hypotensive levels (below 45 Mm. Hg.) for more than 1 to 1.5 hours without showing signs of sudden collapse. The remaining 19 were more resistant and, after 1.5 hours of drastic hypotension, were further bled cautiously until their blood pressure showed a similar tendency to fall precipitously. All the dogs were then sustained by small blood infusions (2–3 cc./Kg.) for an additional 30 to 90 minutes. By this means, it was possible to keep dogs in a state which they otherwise could not maintain over a protracted period.

Restoration of Blood Volume.—At the end of a given period of drastic hypotension the dogs were infused with the remainder of the blood which had been withdrawn during the hemorrhage. Dogs were considered to be irreversible if the infusion resulted in a blood pressure rise which was unsustained and which was followed by a drop to shock levels of hypotension within one to two hours. Dogs were considered to be reversible if their blood pressure rose to, and was sustained at, normal levels for at least two to three hours.

CRITERIA FOR DETERMINING THE STATE OF THE OMENTAL CIRCULATION

The determination of these criteria requires an understanding of the architecture of the capillary bed. Data concerning this appear in our previous publication.[3] In brief, the capillary bed is to be regarded as an interrelated series of specifically functional units, each unit consisting of a central channel leading from arteriole to venule and communicating, by means of side-branches, with the true capillaries. Figure 1 is a diagrammatic sketch of such a unit in a portion of the capillary bed in the omentum together with the nomenclature and characteristics of the various structures.

* The solution had the following constitution in grams per cent in water: Granular gelatin, 1; NaCl, 0.8; KCl, 0.02; $CaCl_2$, 0.02 and $NaHCO_3$ sufficient to bring the solution to p_H 7.2–7.4.

The factors which condition the distribution of blood in the capillary bed act chiefly on the muscular vessels proximal to the capillaries, *e.g.*, the arterioles, metarterioles and precapillaries. Listed below are several criteria associated with these vessels and with the capillaries and muscular venules.

Caliber of Arterioles and Muscular Venules.—Consecutive changes in caliber were always observed on the same vessels and were routinely determined under magnifications of 150 to 210 x by comparing them with the diameter of the red cells. In some cases, the diameters were measured directly by means of an ocular micrometer.

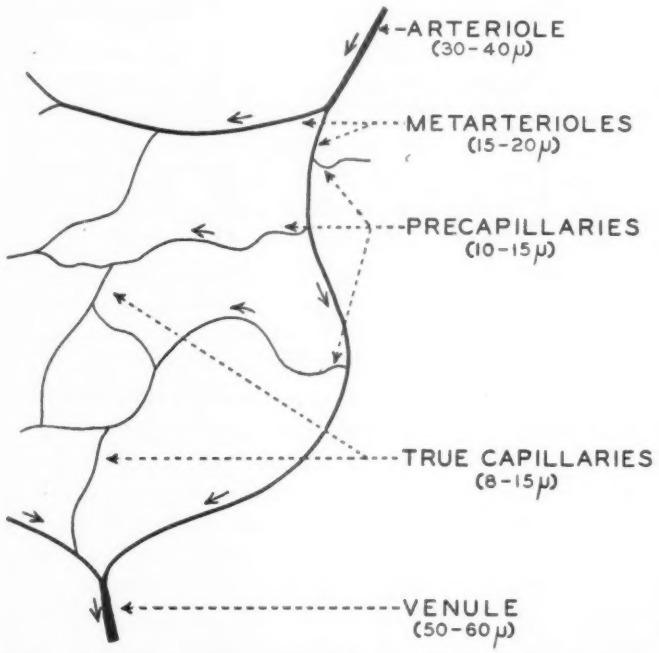

FIG. 1.—Line drawing of a portion of the capillary bed in dog's omentum in which is given the nomenclature used for the different vascular components.

Threshold Constrictor Response to Epinephrine.—This was obtained by applying to the surface of the omentum, three to four drops of epinephrine in gelatin-Ringer's solution. A determination was made of the minimal concentration which temporarily produced a narrowing of a selected metarteriole sufficient to interrupt the blood flow into its precapillary offshoots for not longer than one to two minutes. This was regarded as a threshold response and similar tests were made at intervals throughout the experiment. The omental surface was always thoroughly irrigated between successive tests, which were spaced at least two to three minutes apart. A concentration of epinephrine in gelatin-Ringer's solution of 1:6 to 8 million, on the average, was found to be the normal threshold value for unbled, morphinized dogs.

Vasomotion.—The metarterioles and precapillaries show a characteristic periodicity of alternating dilatations (dilator phase) and contractions (constrictor phase) at intervals of about 20 seconds to three or more minutes. Records were made of several metarterioles and precapillaries before starting the bleedings, and these vessels were kept under observation throughout the experiment. The vasomotion was designated as *augmented* when the rate in periodicity of the dilator and constrictor phases was accelerated and when the duration of the constrictor phase was increased over that of the dilator phase. The vasomotion was designated as *diminished* when the frequency of the periodic movements was reduced and when the duration of the dilator phase became progressively longer than that of the constrictor phase.

Capillary and Venular Flow.—The rate of flow through the true capillaries and venules was noted throughout. Under normal conditions, this flow is so rapid that the individual blood corpuscles cannot be distinguished. The term *"slowed"* is applied to the condition in which the blood cells could be individually distinguished. The term *"sluggish"* is applied when the flow was slowed to such an extent that the blood cells become crowded together. The term *"stagnant"* indicates an almost complete cessation of flow.

Pooling and Trapping.—This indicates an accumulation of blood in regions of the capillary bed which are being by-passed by an active circulation elsewhere in the bed.

EXPERIMENTAL

The dogs were subjected to graded hemorrhage after having been given morphine, and their omenta exposed for microscopic observation. In the earlier experiments, dependence was placed chiefly on the hypotensive levels attained and on their duration. The desired length of the hypotensive period was generally determined by small test infusions. Later, with increasing knowledge of the progressive deviation from the normal condition of the omental circulation, it was found possible to use these as criteria with which to determine the stage when the dog no longer could be brought back to a sustained level of its normal blood pressure by whole blood infusions. The establishment of these criteria is one of the chief purposes of the experiments described in this paper.

Many dogs with a blood pressure of 50 Mm. were found to be in better condition and showed better capillary flow than others with a pressure of 80–85 Mm. Moderate hypotension was determined to be that state in which the capillary flow became significantly slowed with no marked change in the outflow by way of the venules. Drastic hypotension was ascertained by the additional development of a sluggish outflow by way of the venules.

The dogs were classified into three general groups on the basis of differences in their ability to tolerate the blood loss. This is shown in Table I, in which the percentage of blood loss and the duration of the moderate and drastic hypotensive levels are given for each group. When, at

the end of the experiments, the original blood volume was restored, 11 dogs showed a sustained rise of their blood pressure and a complete recovery of their omental circulation for two to three hours after the infusion. The remaining 54 did not respond and died within one to two hours after the infusion.

TABLE I

REACTIONS OF DOGS TO SPECIFIED TYPES OF GRADED HEMORRHAGE

	Resistant Group	Typical Group		Unstable Group	Total No. of Dogs
Blood-loss by per cent of body weight.....	4.0-4.5%	3.0-4.0%	2.0-2.5%		
Duration, in hours, of moderate hypotension*.	3–4 hrs.	3.5–4.5 hrs.	1.5–2 hrs.	2–3 hrs.	
Duration, in hours, of drastic hypotension*...	1.5–3 hrs.	1–1.5 hrs.	2–2.5 hrs.	1–1.5 hrs.	
No. of dogs reversible† to infusion.....	2	6	2	1	11
No. of dogs irreversible‡ to infusion.....	6	28	12	8	54
Total no. of dogs.....	8	34	14	9	65

* Despite variations in the exact level of hypotension, the dogs were kept in a comparable state by regulating the bleeding so as to produce in all the animals the same degree of slowing of the omental circulation.

† By reversible is meant a sustained rise of blood pressure and a recovery of the omental circulation for 2-3 hours after the infusion.

‡ By irreversible is meant a lack of sustained response of the omental circulation and an unsustained rise of blood pressure which lasted not longer than 1-2 hours.

The majority of the 65 dogs, 48 in number (Typical Group) developed circulatory failure after being in the hypotensive state (moderate + drastic) from four to six hours. A smaller number of nine dogs (Unstable Group) proved to be very susceptible to the bleeding and reached hypotensive levels after being bled as little as 1.5 to 2.0 per cent of their body weight. These dogs could not be kept even at moderate hypotensive levels for any extended period of time. Their blood pressure had a tendency to fall despite the restoration throughout a period of two to three hours of their entire blood volume by repeated small infusions. A third small number of eight dogs (Resistant Group) proved to be highly resistant and required bleedings of more than 4 per cent of their body weight to lower their blood pressure to sustained hypotensive levels. These dogs had to be bled repeatedly until a point was reached where their blood pressure tended to fall abruptly. Unless almost their entire blood volume was then restored, they died within 15 to 20 minutes.

The omental changes were essentially the same in the three groups of dogs except for the time required for the different stages to appear and the degree to which the changes developed. The accompanying charts, summarizing the data of four selected protocols of irreversible dogs, illustrate the reactions of eight selected criteria representing the condition of the capillary circulation throughout the syndrome. The extent of deviation from the normal, which is represented by a base line, is expressed by the relative heights of the vertical lines. At the bottom of each chart is a curve of the carotid blood pressure, presented at five-minute intervals. The successive bleedings and infusions are recorded as black squares below the blood pressure curve.

I—TYPICAL GROUP

In this category were the 48 dogs of which the total blood loss amounted to 3 to 4 per cent of their body weight. These dogs were maintained at hypotensive levels for 4.5 to 6 hours, the final one to two hours being at drastic levels (below 45 Mm.). The relative lengths of moderate and drastic hypotension were varied, 34 dogs being subjected to moderate (55–65 Mm.) for 3.5 to 4.5 hours, followed by a period of 1 to 1.5 hours of drastic hypotension (40–50 Mm.), while 14 were subjected to moderate for 1.5 to 2 hours, followed by a relatively longer period of 2 to 2.5 hours of drastic hypotension.

Out of the 48 dogs treated in this way eight recovered after being infused with the blood withdrawn. In these the omental circulation maintained the normal unidirectional flow, although very much slowed during the terminal stage. The vasomotion of the metarterioles and precapillaries disappeared but the epinephrine responsiveness, which became hypernormal during the initial stages after the bleeding, never fell below the normal theshold value obtained prior to the bleeding.

The remaining 40 dogs proved to be irreversible to the final blood infusion. The protocols of two of these, as representatives of this group, are given below, that of Dog 71 being given in detail and that of Dog 64 in part. The times given in the protocols refer back to the zero time at the start of the experiment, as noted in the charts.

A—PROTOCOLS OF DOGS 71 AND 64

Dog 71.—(Chart 1: Wt. 105 Kg. Morphine sulfate, 12 mg./Kg., subcutaneous. Initial B. P., 110–150 Mm. Hg. Omentum exposed 30 minutes later. Capillary circulation slightly hyperemic, returning to normal in few minutes. Metarterioles and precapillaries showed normal vasomotion with phases alternating at intervals of 45 secs. to 2 mins. Threshold response to epinephrine, 1:6 million).

a. *Changes Initial to Hypotensive State (0–1.5 hrs. after start of bleeding).*—The earliest reactions to blood loss occurred while the blood pressure was falling from 110 to 85 Mm. Hg. and are not indicated on the chart. After the first bleeding of 20 cc./Kg. the larger arteries (75–150 μ in diameter) underwent constriction (from 75 to 65 μ). After the second bleeding of 10 cc./Kg. (totaling 3 per cent of body weight) their caliber was further reduced to about one-half to one-third the normal size (45–50 μ). Their accompanying veins constricted after the second bleeding from 100 to 86 μ. These arteries and veins remained constricted throughout the syndrome and relaxed only when the final large infusion was made 6.5 hours later.

The following appears on the chart and deals with the capillary bed proper and with its adjacent arterioles (40–50 μ) and muscular venules (45–60 μ). The reactions of the selected criteria are presented separately in the order of their appearance.

1. *Vasoconstriction.*—The muscular venules (50–60 μ) constricted to 40–45 μ within 15 minutes after the first bleeding. The arterioles (40–50 μ) began to be partially narrowed during the second bleeding (from 40 to 30 μ) and, by the time the blood loss had reached a total of 3 per cent, became further constricted to 20 μ and varicose. This was the maximal constriction observed during the syndrome.

2. *Vasomotion.*—That of the metarterioles was augmented shortly after the second bleeding. By the end of the first hour, the constrictor and dilator phases alternated as

rapidly as two complete cycles per minute. During the second hour, the vasomotion of the precapillaries was especially prominent.

3. *Response to Epinephrine.*—The responsiveness to epinephrine rose at about the same time that vasomotion became augmented. After the second bleeding the threshold response was 1:13 million.

4. *Capillary Flow.*—There was little change in the rate of flow although the flow became increasingly intermittent during the second hour in accordance with the augmented vasomotion.

5. *Venular Flow.*—This remained almost unchanged. After the third bleeding many of the direct shunts between arterioles and veins became considerably narrowed. There was a definite slowing of the flow in the larger veins.

b. *Changes during Hypotensive State after Third Bleeding (1.5–6.5 hrs. after start of hemorrhage. B. P., 65 Mm. Hg.).*—The progressive changes in the capillary bed during the remainder of the posthemorrhagic syndrome could conveniently be divided into three stages. When the blood pressure fell to moderate hypotensive levels, there was an appreciable slowing of the flow but the *hyperreactive* aspects of the syndrome continued for about four hours, during which 2 cc./Kg. was infused to hold the blood pressure within the range of 55–65 Mm. after four hours of moderate hypotension. The blood pressure was further lowered by a small bleeding. This introduced a more severe curtailment of flow and the development of a *transitional* stage in which the hyperreactivity of the vessels was gradually lost over a period of about an hour. Finally, during the last half hour of drastic hypotension and for 20 minutes after the final infusion of whole blood had been started, the syndrome passed into a *hyporeactive* stage.

HYPERREACTIVE STAGE

1. *Vasoconstriction.*—The arterioles maintained the constricted state noted during the early compensatory reactions. The venules remained moderately narrowed until the beginning of the fourth hour, when they began to distend from 40 to 45 μ.

2. *Vasomotion.*—The augmentation attained one cycle every 15 to 20 seconds, with the constrictor phase lasting about two-thirds of each cycle. Towards the end of the fifth hour, the length of the dilator phase became progressively increased.

3. *Response to Epinephrine.*—During the last hour of this stage (6th hour) the hyperreactivity of the metarterioles and precapillaries fell slightly from 1:13 million to 1:10 million.

4. *Capillary Flow.*—During the third and fourth hours the rate of flow remained unchanged. Most of the flow was restricted to the central channels by the constriction of the precapillaries.

5. *Venular Flow.*—The venular flow began to fall off within 30 minutes and diminished appreciably toward the end of the fifth hour.

TRANSITIONAL STAGE

1. *Vasomotion.*—That of the metarterioles diminished, the dilator phase becoming increasingly longer and the constrictor phase very short.

2. *Venular Caliber.*—The venules (45–60 μ) became dilated from 45 μ to 65 μ and exhibited markedly thin walls.

3. *Venular Flow.*—This became increasingly sluggish.

4. *Capillary Flow.*—A marked slowing became evident, especially during the fifth hour. This was accompanied by a developing deficiency of outflow through the venules. The diminished vasomotion of the metarterioles and the longer periods of dilatation of the precapillary sphincters were accompanied by an increase in the number of capillaries containing a flow. This increased distribution of blood, without a corresponding increase of the amount of inflow, resulted in a significant slowing of the flow, especially on the venous side of the bed, which was intensified by the atonic state of

the muscular venules. The flow in the larger omental veins became considerably reduced and was now maintained mostly by the few arteriovenous anastomoses which still were open.

5. *Response to Epinephrine.*—Within 20 minutes after the curtailment of the capillary flow this fell from the hyperreactive response of 1:10 million to a relatively normal response of 1:4 million.

HYPOREACTIVE STAGE

1. *Vasomotion.*—This ceased in the metarterioles with the dilator phase persisting. That of the precapillaries stopped 20 minutes later.

2. *Response to Epinephrine.*—There was only a fleeting constrictor response to 1:2 million.

3. *Venules and Venular Capillaries.*—These became distended by backflow from the congested veins.

4. *Arterioles.*—The relaxation of the arterioles developed later than in the venules and the previously very slow forward flow was replaced by a pulsatile movement of the blood.

5. *Stagnation of Blood.*—Many of the capillaries and venules were stagnant.

c. *Changes Following Restoration of Blood Volume by Infusion.*—At this point (after 4.5 hours of moderate and 1.5 hours of drastic hypotension) a drip infusion was started and continued until all of the blood previously withdrawn had been restored. During the 30 minutes that the infusion lasted the blood pressure rose to 90 Mm. Hg. When about 8–10 cc/Kg. (one-third of the blood to be infused) had been given, the constricted omental arteries gradually resumed and maintained their normal caliber. The larger veins relaxed at about the same time but became abnormally dilated during the ensuing 50–60 minutes. The blood pressure then again fell to hypotensive levels.

There was no improvement in the peripheral circulation until about 20 minutes after the infusion was started and the blood pressure had risen to about 80 Mm. Hg. At this time the capillary flow became moderately speeded but slowed down again after 40–50 minutes. The previously dilated arterioles became slightly constricted* and there was a faint return of vasomotion of the metarterioles. The epinephrine response to 1:4 million became more evident than before, and this degree of responsiveness lasted for 30 minutes when it fell off rapidly.

About one hour after termination of the blood infusion, while the blood pressure was still about 70–80 Mm. Hg., the capillary flow began to slow down and became almost completely stagnant as the blood pressure slowly dropped below 70 Mm. Backflow from the larger veins into the capillary bed now became prominent and a generalized stagnation occurred with the death of the dog.

Dog 64.—(Chart 2: Wt. 9 Kg. Morphine sulfate, 12 mg./Kg., subcutaneous. Initial B. P., 120–130 Mm. Hg.).

The omental changes in the chart of Dog 64 were closely similar to those of Dog 71. This protocol is presented because it illustrates particularly well that blood pressure and peripheral circulatory curtailment do not go hand in hand. Between the fourth and fifth hours, when the blood pressure was relatively high, varying between 65 and 80 Mm., there was a decided slowing of the capillary flow and a more drastic slowing of the venular flow. A similar circulatory curtailment in Dog 71 did not occur until the blood pressure had dropped to 50–55 Mm. Hg. Moreover, later, during the fourth

*Only occasionally do the arterioles in the irreversible stage of shock respond to the infusion by a temporary moderate constriction, as in the above case. As a rule, the dilatation of the arterioles is one of the final evidences of irreversibility, and, following infusion, they become still further dilated.

and fifth hours, when blood infusions of 3–4 cc./Kg. were given, the venular caliber, vasomotion, venular and capillary flow remained subnormal despite the temporary rise of the blood pressure by 20–30 Mm. which occurred with each infusion. During the sixth and seventh hours the infusion of all the blood withdrawn (by three separate injections) had no appreciable action on the peripheral circulation, although it kept the blood pressure from falling precipitously.

CHART 1

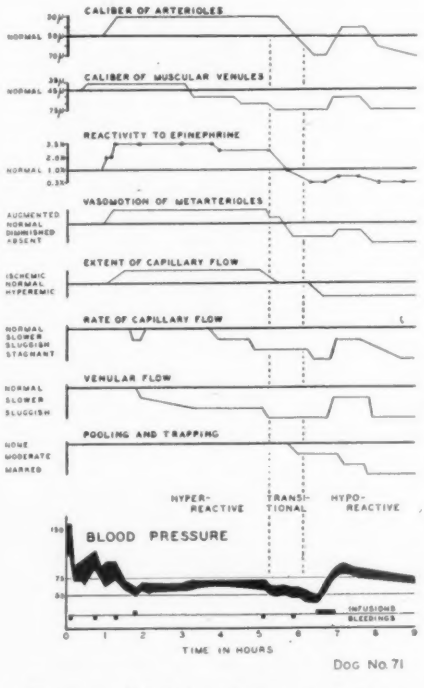

CHART 2

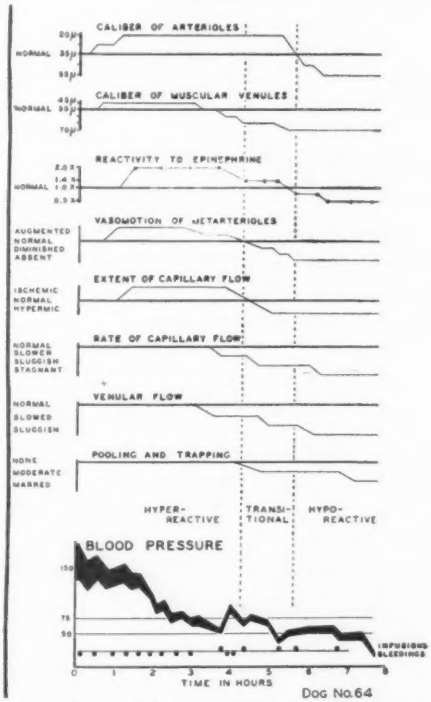

CHART 1.—Tabulation of protocol of Dog 71, representing typical group. The chart shows the changes in the capillary bed of the omentum in their relations to blood pressure, bleedings and infusions in a dog which became irreversible to infusion of the blood withdrawn. The upper eight rows represent changes in selected functional criteria.

The deviations from the normal are expressed by the relation of a continuous graph line to the normal base line. In all the criteria, except for epinephrine reactivity, this represents changes recorded continuously by direct observations. The epinephrine reactions were obtained at intervals, and each is recorded on the chart by a solid circle.

The blood pressure curve represents carotid readings at five-minute intervals, each with maximum and minimum values obtained during a 30-second period. The horizontal lines at 75 and 50 Mm., respectively, represent shock levels of hypotension.

CHART 2.—Tabulation of protocol of Dog 64, also of typical group. It illustrates the unreliability of blood pressure as a criterion of circulatory changes. Explanatory legend same as in Chart 1.

B—ANALYSIS OF CHANGES IN OMENTAL CIRCULATION IN DOGS OF THE TYPICAL GROUP

The two protocols, prepresenting the 40 irreversible dogs of this group, demonstrate that definite circulatory changes occur as the hemorrhagic syndrome progresses towards irreversibility. In all the cases, the initial large bleedings of 2 to 3 per cent of body weight were accompanied by a vasoconstriction of the larger arteries and veins and a restriction of the omental circulation with an augmented vasomotion of the metarterioles and precapillaries. Throughout this period the epinephrine reactivity was hyper-

normal and, in some cases, rose from a normal threshold level of 1:4 to 6 million to as high as 1:60 million. This hyperreactive state generally persisted for three to five hours after the initial bleedings.

During the period of hypotension, the subsequent small bleedings were followed not only by the mechanical factor of a pronounced slowing of the flow but also by a progressive deterioration of the functional aspects of the bed. The earliest manifestation of this was venular dilatation. The other outstanding effects, *viz.*, diminution of the vasomotion and the fall of epinephrine responsiveness, varied as to time and degree in different dogs and are discussed below.

The majority which tolerated a total blood loss of 3 to 4 per cent and a relatively long period of moderate hypotension resembled Dogs 71 and 64. This was also the case for six of the 14 dogs with a short moderate hypotension which were bled expressly to bring them into drastic hypotension. The remaining eight showed a spontaneous tendency for the blood pressure to fall and did not require bleeding to bring them early into drastic hypotension. These eight maintained the vasomotion and the normal epinephrine reactivity of their metarterioles almost to the time of death, thus indicating that at least some of the physiologic properties of the capillary bed had not deteriorated. Their circulatory failure presented essentially the effects of a mechanical type. The ensuing circulatory failure may be attributed, in large part, to a marked trapping and pooling of blood in the capillary bed.

A few relatively unstable dogs were maintained at low hypotensive levels of 40 to 50 Mm. for as long as 2 to 3.5 hours by repeated small infusions (3-4 cc./Kg.). In spite of the infusions, the blood persisted in pooling and stagnating in the peripheral circulation and there developed a backflow into the capillaries which finally became so intensified as to prevent the return of adequate amounts of blood from the tissues. With this type of extreme hypotension the syndrome became irreversible to infusion. Although neither the epinephrine reactivity nor the vasomotion was completely depressed, the restoration of the blood withdrawn did not bring the stagnant blood in the bed into active circulation and the dogs died within 20 to 40 minutes after the infusion.

Another interesting feature was the variation in the effect of the sustaining small infusions on the recovery of some of the physiological functions of the capillary bed. Dog 64 was an example of those cases in which the small infusions exerted no appreciable effect on the capillary bed. However, in other dogs, the capillary bed did react, particularly in regard to the epinephrine reactivity, which rose temporarily, although progressively less, with each sustaining infusion. Vasomotion, on the other hand, when once subnormal was never observed to recover as long as the hypotension remained at drastic levels.

II—UNSTABLE GROUP

This included nine dogs which were unusually susceptible to bleeding. Considerable care had to be taken while bringing them into hypotensive levels

to prevent a precipitous fall of their blood pressure. They also had to be frequently primed with small infusions in order to maintain them in hypotension for any extended period. Only one of the nine dogs was found to be reversible by blood infusion. This dog had stopped breathing and required a massive blood infusion before respiration reappeared. The depressed omental

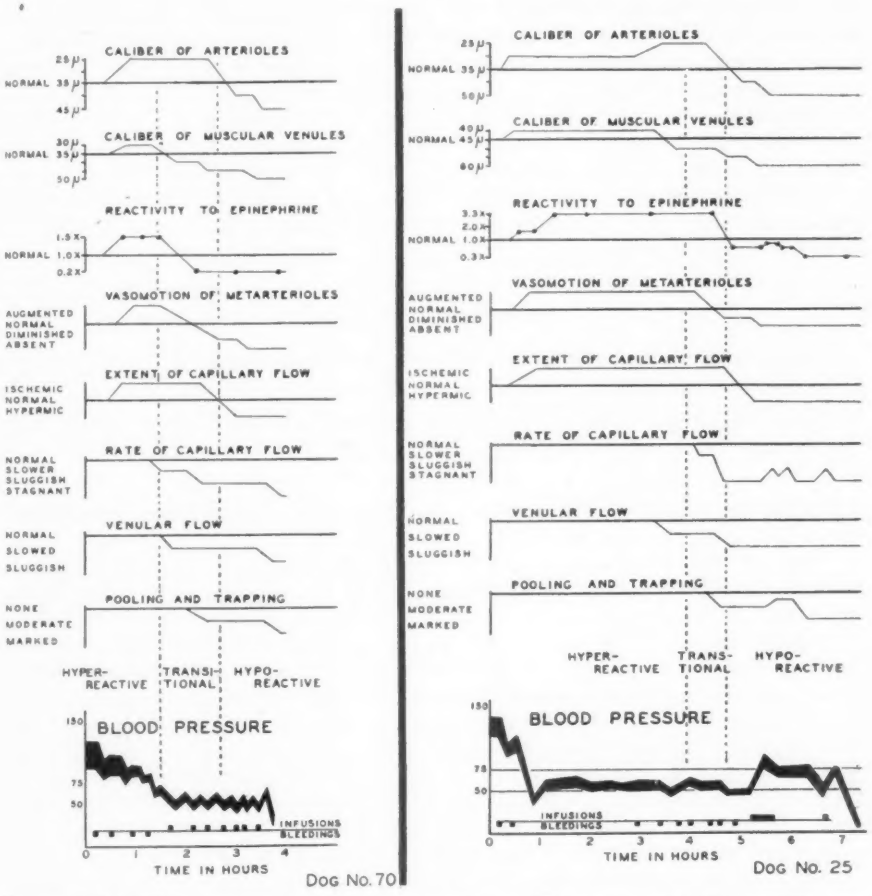

CHART 3.—Tabulation of protocol of Dog 70, representing unstable group. Explanatory legend same as in Chart 1.

CHART 4.—Tabulation of protocol of Dog 25, representing resistant group, which requires frequent bleedings. Explanatory legend same as in Chart 1.

circulation was restored to normal within 15 minutes after the infusion had been made.

Dog 70.—(Chart 3: Wt. 12 Kg. Morphine sulfate, 12 mg./Kg., subcutaneous. Initial B. P., 95–120 Mm. Hg.).

Prior to bleeding the epinephrine response was 1:4 million and the vasomotion recurred one cycle in two to three minutes. A blood loss of 285 cc. (2.38 per cent of body weight) in four bleedings brought the blood pressure down to the 60–67 Mm.

range and appreciably slowed the flow through the bed. Within 1.5 hours after these bleedings the hyperreactive aspects of the circulation were disappearing. The venules became atonic and distended as early as the end of the second hour. Both the epinephrine reactivity and vasomotion, which had been only moderately enhanced, fell off rapidly during the early part of the third hour. The cessation of vasomotion was followed by an almost complete stagnation of the capillary flow. These changes rapidly produced a pooling and trapping of blood on the venous side of the bed as early as 2.5 hours after the initial bleedings and after only one hour of hypotension. Throughout the third and fourth hours, seven infusions of whole blood, each about 3 cc./Kg., were required to keep the dog from precipitously going into circulatory collapse. Although these temporarily sustained the blood pressure, none exerted any beneficial action on the peripheral circulation. Respiratory failure occurred during the latter half of the fourth hour, necessitating artificial respiration. The hyporeactive state persisted despite the infusion of the final 70 cc. of blood and complete circulatory collapse occurred at the end of the fourth hour. Throughout the final 60 to 70 minutes, the omental circulation was practically at a standstill, except for a sluggish flow in the largest arteries and veins.

III—RESISTANT GROUP

This included eight dogs which were highly resistant and required repeated bleedings to counteract the tendency of the blood pressure to rise out of the hypotensive range. The following is a summary of the protocol of Dog 25, which was selected as representative of this group.

Dog 25.—(Chart 4: Wt. 10 Kg. Morphine sulfate, 12 mg./Kg., subcutaneous. Initial B. P., 130–140 Mm. Hg.).

A blood loss of 3 per cent of the body weight brought the blood pressure down to moderate hypotension (55–65 Mm.) which persisted for over two hours. Throughout this period the flow through the bed was rapid, although restricted to the central channels by the hyperactivity of the vasomotion. At the beginning of the third hour, the blood pressure showed a tendency to rise, and during the ensuing two hours seven bleedings, of 2 to 3 cc./Kg. each, had to be made to prevent it. Deterioration of the capillary circulation did not develop until after the fourth hour, when the capillary blood flow began to slow down. Within the next 40 minutes, all of the selected features were depressed below normal. Two small bleedings (3 cc./Kg.) brought the blood pressure to drastic levels of hypotension (42–52 Mm.), and the capillary circulation to a sluggish state. This brought about chiefly a marked pooling of blood in the venules. At this point (after 4.5 hours of hypotension) an infusion, restoring the blood volume (39 cc./Kg.), raised the blood pressure but had no sustained beneficial action on the peripheral circulation. The blood pressure remained above 70 Mm. for about 1.5 hours, when the dog went into cardiac and respiratory failure and died. Such animals are extremely difficult to recover by infusion.

Discussion.—A prerequisite for any experimental study of the capillary circulation is the establishment of adequate criteria for determining the normal functional state of the vascular bed. Too much stress cannot be placed on the necessity of rigid adherence to precautionary measures for preventing the observational technic from interfering with the normal reactivity of the sensitive, organized systems of the capillary bed. A discussion of such measures is given in a previous publication.[8]

The omentum was elected in the present study because, in contrast to the cutaneous tissue, its circulation is maintained throughout the greater part of the hemorrhagic syndrome. It has been claimed, because of the pale and ischemic appearance of the omentum at autopsy, that this structure is not the logical site for the study of significant vascular changes in circulatory collapse. On the other hand, in the present study, the successive changes in the omental circulation have been shown to serve as an excellent end-point for evaluating the progressive nature of the syndrome. No attempt has been made at an analogy between the circulatory changes observed in the omentum and those occurring in other tissues. However, the findings are suggestive in that they bring out the type of change occurring in a typical capillary bed as a result of the ischemia produced by hemorrhage. In previous studies[6] on the frog and mouse it was shown that the type of capillary bed described in this paper is characteristic of those in the skin, striated muscle, intenstinal submucosa and the pancreas. Hence although the omental changes may not be of direct significance in precipitating the circulatory failure, in all likelihood they reflect conditions which occur in other organs where such changes may be of paramount importance.

Wiggers[14] recommends that whenever possible a differentiation be made between initiating and consequential mechanisms during the shock syndrome. The results presented in this paper, insofar as the capillary bed is concerned, point to the appearance, in succession, of two outstanding mechanisms leading to so-called irreversible hemorrhagic shock. The initiating mechanism is that of widespread vasoconstriction, which follows immediately and is proportional to the blood loss. The consequential mechanism consists of a series of changes which result from the curtailment of the blood flow through the capillary bed.

The initiating mechanism of vasoconstriction is well recognized and, by some, has been taken as the prime feature in shock. Vasoconstriction in the microscopic vessels of the skin following hemorrhage has been observed in dogs by Meek and Eyster,[9] and Mann,[10] in rabbits by Levinson and Essex,[11] and in rats by Chambers, Zweifach and Lowenstein.[12] In our present study on the dog's omentum, vasoconstriction was also observed only when the blood loss amounted to about 3 to 3.5 per cent of the body weight.

On the basis of changes in the capillary circulation following hemorrhage it was possible to distinguish between two discrete types of peripheral circulatory failure. In our[16] studies on acute hemorrhage it was shown that the initiating mechanism of excessive and rapid blood-loss is emphasized to such a degree that circulatory collapse occurred without the development of other consequential mechanisms in the capillary bed. This involved a purely mechanical type of circulatory failure in which vasoconstriction of the larger blood vessels and lowered blood pressure by themselves produced the semi-stagnation of the flow and the pooling of blood in the capillary bed. This type of circulatory failure is completely reversible by adequate blood infusion.

Our data on the effects of acute hemorrhage conform with the results

of Page and Abell[2] from their experiments on circulatory failure in dogs and cats caused by the acute removal of blood. They obtained similar results with the use of the venous tourniquet and generalized that circulatory failure in shock is primarily a result of excessive vasoconstriction. They, thus, considered the initiating mechanism as the only important factor in shock. However, it should be noted that their tourniquet experiments involved venous ligatures on all four limbs. This induces considerable swelling of all the limbs and the results could be interpreted from the same point of view of excessive fluid loss as obtains in acute hemorrhage.

The introduction of consequential factors in hemorrhagic shock occurs by maintaining the dogs, through the use of small infusions, in a state in which a sluggish capillary circulation persists over a protracted period of time. The ensuing type of circulatory failure involves a progressive deterioration of those mechanisms which maintain the functional integrity of the capillary bed. From our observations on the omentum it was found that, with graded hemorrhage, the initial, compensatory hyperreactivity of the syndrome persists as long as the blood pressure does not fall below the level needed to maintain a continuous peripheral flow. The consequential mechanism producing the hyporeactive stage comes into play when the blood pressure is maintained for at least 2 to 2.5 hours at levels at which the capillary circulation is slowed sufficiently to impair the outflow through the venules.

In the present study dependence was placed on the duration rather than on the degree of hypotension required to bring about irreversibility. Our results indicate that this produces a more standardized type of shock, and agree with the findings of Wiggers and Werle.[17] With the omental circulation as a guide, the syndrome was further standardized by bleeding all of the dogs until the flow through the capillary bed was significantly retarded, but not stagnant. The maintenance of this condition for two to three hours set into play local mechanisms which, under normal conditions, would act to increase the blood flow through the tissue (diminished vasomotion with the dilator phase predominating, reduced responsiveness to epinephrine, thereby presumably reducing the response of the muscular elements of the capillary bed to nervous stimuli, and the opening up of numerous capillary channels to the circulation). These changes in the capillary bed may be attributed to the piling up of metabolites in the tissues. Moreover, when the supply of blood and the propelling force are deficient, the opening up of the capillary bed for the reception of increased amounts of blood aggravates the general situation. The result is twofold: The drainage of the blood from the capillary bed continues to be faulty; and the inadequate and severely strained hemodynamic set-up is subjected to further strain by having a greater number of vessels through which to drive the blood. These conditions serve to bring about a further disorganization of the peripheral circulation, a prominent feature of which is atony of its muscular components. A vicious cycle of events is thus initiated through the interaction, on the one hand, of a trapping

and pooling of blood in the peripheral vessels and, on the other, of a disturbed metabolism of the tissues.

The terms "trapping" and "pooling" have been used to denote the progressive sequestration of blood from the active circulation. Fine, Seligman and Frank,[18] using radioactive tagged plasma-proteins, have offered evidence that the "lost" blood in the syndrome is sidetracked into inactive capillary vessels and not lost through increased capillary permeability. Our studies offer visual evidence for this and indicate that trapping and pooling develop on the venous side of the capillary bed during the hyporeactive stage of the hemorrhagic shock syndrome. Trapping occurs as a result of the inadequate driving force for propelling the blood through all of the vessels, so that appreciable amounts of blood are left to stagnate in many capillaries which are by-passed by the active circulation. Pooling occurs subsequently with the failure of the most important peripheral, integrative factor of the capillary bed, *viz.*, the vasomotion of the metarterioles and of the precapillaries. The capillary bed now becomes an inert network of vessels with no active rôle in the distribution of blood and in its return from the tissues.

With the loss of the integrative functional activity of the capillary bed, the outflow of blood through the venules becomes disproportionately reduced with respect to the arteriolar inflow. There thus accumulates in the capillary bed an ever-increasing proportion of the blood. The trapping and pooling, though small, are sufficient to intensify the oligemia until circulatory collapse ensues. This pooling does not necessarily indicate the accumulation of more than the normal amount of blood in the capillary bed, the amount at death being actually less than that normally present.

Circulatory collapse, following the development of hyporeactivity in the irreversible dogs, is essentially the result of a discrepancy between the volume of the circulating blood and the capacity of the vascular system. The changes in the omentum suggest two possible mechanisms which can take part in precipitating the circulatory failure. These are illustrated in Chart 5, which is a diagrammatic presentation of the outstanding changes representative of all the dogs studied. One set of changes emphasizes an intensification of the oligemia through pooling and trapping in the capillary bed (note sequence of changes on right side of the figure). The other set of changes intensifies the oligemia by an increase in the capacity of the vascular tree through the deterioration of the peripheral mechanisms for restricting the blood flow through the capillary bed (note sequence of changes on left side of the figure). When a group of dogs are bled, so as to produce circulatory failure, both types of circulatory changes develop, regardless of the hemorrhagic procedure used. The mechanical type of failure predominates when the degree of hypotension and the blood-loss factor are emphasized. On the other hand, the hyporeactive type of failure predominates when, as in the present study, the duration of hypotension is emphasized.

SUMMARY

Characteristic indices in the capillary bed of the omentum of dogs subjected to graded hemorrhage under morphine have made it possible to identify successive stages of the syndrome leading to a state in which the dogs become irreversible to the restoration of their blood volume with whole blood. These stages are an initial hyperreactive stage, an intermediate transitional stage and a terminal hyporeactive stage.

Under the conditions of generalized ischemia during hemorrhagic shock, the vessels of the capillary bed undergo progressive physiologic changes expressed by an inactivation of the muscular vessels of the bed, with loss of their responsiveness, and a disorganization of the peripheral circulation.

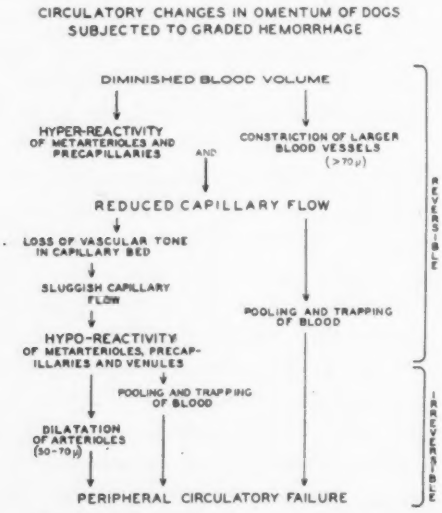
CIRCULATORY CHANGES IN OMENTUM OF DOGS SUBJECTED TO GRADED HEMORRHAGE
DIMINISHED BLOOD VOLUME
HYPER-REACTIVITY OF METARTERIOLES AND PRECAPILLARIES
AND
CONSTRICTION OF LARGER BLOOD VESSELS (>70 μ)
REDUCED CAPILLARY FLOW
LOSS OF VASCULAR TONE IN CAPILLARY BED
SLUGGISH CAPILLARY FLOW
HYPO-REACTIVITY OF METARTERIOLES, PRECAPILLARIES AND VENULES
POOLING AND TRAPPING OF BLOOD
DILATATION OF ARTERIOLES (50-70 μ)
POOLING AND TRAPPING OF BLOOD
PERIPHERAL CIRCULATORY FAILURE
REVERSIBLE
IRREVERSIBLE

CHART 5.—On right side of chart are indicated changes resulting from extreme blood-loss (greater than 4% of body weight) with little or no hyporeactivity. On left side of chart are indicated changes resulting from less extreme blood-loss (3-4%) with development of a hyporeactive state before circulatory failure.

This is in contrast to the reactions of the larger blood vessels, which maintain an active state of constriction until shortly before death.

It was possible to distinguish in the capillary bed between two clear-cut types of changes during the progress of the syndrome. The first involves a purely mechanical factor which arises from the lowered blood pressure and from the vasoconstriction of the larger blood vessels. The absence of a sufficient propelling force induces a marked slowing of the capillary flow and the pooling of blood in the bed. This is characteristic of rapidly induced drastic hypotension and tends to be reversible to the restoration of the blood lost. The second type, which occurs when the drastic hypotension is sufficiently prolonged, involves a progressive deterioration of the functional

integrity of the capillary bed, *i.e.*, loss of arteriolar and venular tone, of vasomotion, and of responsiveness to epinephrine.

CONCLUSIONS

From our observations on the peripheral circulation of the omentum, a significant finding is that the development of irreversibility to infusion is associated with a hyporeactive state of the functional aspects of the capillary bed. The hyporeactivity *per se* does not necessarily imply irreversibility. The hyporeactivity must be maintained for a protracted time. The actual end-point indicating irreversibility is the failure of the hyporeactive capillary circulation to respond to test infusions. Restoration, at this stage, of all the blood previously withdrawn may mechanically set up a flow through the bed but will not restore the physiologic reactivity of its muscular components. The significance of the changes observed in the capillary bed is further demonstrated by the fact that they reflect the progressive deterioration of the animal throughout the hemorrhagic shock syndrome.

We wish to acknowledge the very able assistance of our laboratory technician, Leon Dziorney.

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CONDYLOMATA ACUMINATA

TWO HUNDRED CASES TREATED WITH PODOPHYLLIN

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CONDYLOMATA ACUMINATA not only are pathologic "nuisances" but occasionally they reach proportions which constitute serious clinical problems. Reliable statistics regarding their incidence are not available but it is generally agreed that they are extremely common. The fact that 180 individuals with typical lesions were seen by us during the past nine months adds proof to this contention. The great variety of therapeutic measures which have been recommended illustrates the inadequacy of most methods of treatment. The purpose of this report is to present the dramatic results which we have obtained with podophyllin. There is reason to believe that this drug may be a "specific" for condylomata acuminata.

The etiology of these growths remains unknown. They present raspberry, cauliflower or cockscomb masses, which are soft, red or cyanotic, often friable, and may be sessile, pedunculated or attached by a broad base. They must be differentiated from carcinoma and condylomata lata of syphilis, but this usually is not difficult. Mixed lesions may occur and complicate the clinical picture.

Condylomata acuminata have been described in many locations, usually on or near the genitalia, and have been given the misnomer "venereal warts." In the present series, they were found on the penis, the labia, the fourchette, lining the vagina, at the urethral meatus, around the anus, on the perineum and on the scrotum (Table I). They had been present for one day to eight months, with the average duration three months. All of these patients were less than 36 years of age, and 90 per cent were white.

Podophyllin is a powder which varies in color from light brown to greenish-yellow, and turns darker when subjected to heat or light. It is an irritant and active purgative and is the basis of several proprietary "liver pills." Various strengths of podophyllin have been tried in the treatment of condylomata acuminata but a 25 per cent suspension in mineral oil has proved most efficacious and has been used in the 200 cases which comprise this report.

The podophyllin in oil is applied with a cotton swab to the surface of the lesions. This is a painless procedure and there is no immediate reaction. Anesthesia is not required, because of the viscosity of the oil and close approximation of normal tissues (*e.g.*, redundant prepuce) it is impossible to keep the podophyllin confined to the condylomata, but in most instances this does not alter the therapeutic effect of the drug. Within

a few hours the growths become blanched, and 24 to 48 hours later they appear necrotic. The condylomata begin to slough on the second or third day and promptly disappear. No ulceration or scarring is left at the bases. The adjoining normal tissue usually is unaffected even though it has been exposed to the same medication. Most patients experience no discomfort during the entire process and only rarely is sedation necessary. There have been no systemic reactions to any of the 249 treatments employed in this group of 200 patients. This type of therapy is so simple and the clinical courses so uneventful that it is performed in the clinic or office and hospitalization is unnecessary. The minimum loss of time to the patient has made it especially valuable among military personnel.

No satisfactory explanation of the more or less specific action of podophyllin on the condylomata is possible at this time. The most logical assumption is that the irritating power of the drug produces spasm of the small vessels, which in turn causes ischemia, necrosis and sloughing. The blood supply of the condylomata apparently is more susceptible to the 25 per cent suspension than that of the more viable, adjoining, normal tissues. The podophyllin also seems to dehydrate the condylomatous masses. Irrespective of the exact physiology involved, the dramatic results obtained in these cases indicate that podophyllin is of tremendous value in the treatment of condylomata acuminata.

All of the 200 patients in this study were cured regardless of the number, size, location or duration of the growths. Only one application of podophyllin was needed for 81.5 per cent, while an additional 14.5 per cent were cured by a second treatment. No one required more than four applications of the drug. In 72.5 per cent of the cases, complete recovery occurred within four days, while only 6.5 per cent required more than eight days for disappearance of the growths. No discomfort was experienced by 83.5 per cent of the patients and only 2 per cent required any sedation (Table I).

Because of the movements of military organizations, complete follow-ups have been impossible. There have been nine known recurrences of the condylomata (4.5 per cent) but others may have occurred. In each of these nine cases, response was prompt to additional similar treatment with podophyllin. Inasmuch, as the etiology of the initial lesions is unknown, there is reason to anticipate recurrences or new growths after *any* type of therapy. The causative factors no doubt continue to exist in many cases despite prompt disappearance of the original growths. Initial and recurrent lesions respond equally well to podophyllin, and this appears to be the treatment of choice for all condylomata acuminata.

The minor variation in clinical courses with lesions in different locations are demonstrated by the following group analyses (Table I):

Penis.—A total of 168 patients had condylomata acuminata on the penis. The only instances of associated venereal diseases were in this group. Nine patients had acute gonococcal urethritis and five had chancres. These were

treated by accepted methods and did not influence the course of the condylomata or result in recurrence.

The number of growths in each case varied from single lesions to clusters of as many as 25 pedunculated tumors with the average six. These varied in size from 2 Mm. in diameter to conglomerate masses covering the glands or filling the coronal sulcus. Most of the discrete lesions were 0.5 to 1.0 cm. in diameter.

TABLE I

ANALYSIS OF 200 CASES OF CONDYLOMATA ACUMINATA TREATED WITH PODOPHYLLIN

		No. of Treatments				Days Until Cured			Pain			V. D.		
Location	Total Cases	1	2	3	4	2–4	5–8	More	None	Mild	Req. Sed.	Lues	GC.	Recurrence
Penis.....	168	148 88.1%	16 9.5%	2	2	134 79.8%	30 17.8%	4	150 89.3%	18 10.7%	0	5	9	8
Female genitalia...	15	9 60%	6 40%	0	0	7 46.6%	4 26.7%	4	2 13.3%	9 60%	4	0	0	0
Urethra.....	10	2 20%	5 50%	2	1	2 20%	5 50%	3	10 100%	0	0	0	0	1
Anus.....	4	3 75%	0	0	1	1 25%	2 50%	1	2 50%	2 50%	0	0	0	0
Male perineum..	2	1 50%	1 50%	0	0	1 50%	0	1 50%	2 100%	0	0	0	0	0
Scrotum.....	1	0	1 100%	0	0	0	1 100%	0	1 100%	0	0	0	0	0
Total...	200	163 81.5%	29 14.5%	4 2%	4 2%	145 72.5%	42 21%	13 6.5%	167 83.5%	29 14.5%	4 2%	5 2.5%	9 4.5%	9 4.5%

The condylomata were found most frequently in the coronal sulcus or at the frenulum but occurred at any point along the shaft or mucous membrane of the redundant prepuce (Fig. 1). Four patients had been circumcised prior to the onset of the lesions, thus dispelling any claims that circumcision alone is adequate prophylaxis. Twenty patients had been treated previously with escharotics without complete disappearance of the growths.

Only one application of podophyllin was necessary to produce complete disappearance of all lesions in 88.1 per cent of these patients (Fig. 2). Only four patients required more than two treatments. An interval of four to six days was employed between applications in these cases.

The condylomata had entirely disappeared and the sites appeared normal within four days in 79.8 per cent of the patients (Fig. 2). An additional 17.8 per cent were well in five to eight days. Those patients who required repeated treatment automatically had longer intervals until cured.

No discomfort of any kind was noted by 89.3 per cent of the patients. The remaining 10.7 per cent had only mild burning. None of these required sedatives. The same patients (total of 18) had some degree of chemical balanoposthitis. All had very long prepuces. The balanoposthitis was mild and subsided quickly in all but three cases. The tissue reaction was severe in these three instances and, because of marked prepucial edema, dorsal slit was done. This may not have been absolutely necessary. In each of

these three cases complete disappearance of the condylomata was found at operation and the balanoposthitis subsided promptly after surgical exposure of the glans. No balanoposthitis or edema has been observed since the patients have been advised to wash off the podophyllin 24 hours after its application.

Eight of our nine known recurrences were in this group. These appeared

FIG. 1

FIG. 2

FIG. 1.—Multiple condylomata in coronal sulcus and along mucous membrane of prepuce. (Photograph by U. S. Army Signal Corps)

FIG. 2.—Same patient four days after single application of podophyllin in oil. (Photograph by U. S. Army Signal Corps)

from one to six months later and in each case, one additional treatment caused disappearance of the lesions. Several patients have been followed nine months without recurrence or new growths.

Hospitalization was necessary only for the three patients who were subjected to dorsal slits.

Female Genitalia.—Fifteen women had condylomata acuminata on the genitalia. Eight of these were pregnant. The growths have been known to fill the vagina and require cesarean section. This promised to be true in at least one of this group.

The lesions were confined to the labia in nine cases, to the fourchette in two patients and were scattered throughout the vagina in the remaining four. They varied in size from 0.5 cm. in diameter to a condylomatous mass which filled the vagina of one patient who was eight months pregnant. In most instances four or five growths were present.

No patient in this group required more than two applications of podophyllin and 69.3 per cent were cured within eight days. The remaining four patients had disappearance of the condylomata in 9 to 14 days.

These patients experienced more pain than any other group. The four with diffuse vaginal involvement required codeine or morphine. Only two

patients, with lesions limited to the labia, had no discomfort. Sedation was necessary for only 12 to 24 hours.

No recurrences have been noted. Treatment of the condylomata did not disturb any of the eight pregnancies.

Urethra.—Ten males had single lesions just inside the urethral meatus. These were 0.2 to 0.6 cm. in diameter. Only two were cured by one treatment. Urination caused premature removal of the podophyllin from the condylomata, thereby, necessitating repeated applications of the drug. Five patients were well after two treatments. Two patients required three applications and another needed four. An interval of four days was used between treatments.

Because of the prolonged therapy, only two patients were cured within four days. Five were well in five to eight days and the remaining three patients had disappearance of the growths in 9, 14, and 21 days, respectively. None of these ten patients had any pain.

One patient, whose condyloma disappeared after a single treatment, had a recurrence two months later. This disappeared after two treatments.

Anus.—Four males had clusters of condylomata surrounding the anus at the mucocutaneous margin. Three were cured within one week after a single application of podophyllin. The fourth patient required four treatments, and was well in 16 days.

Two patients had no discomfort but the other two had mild burning pain for 24 hours. No recurrences have been observed in this group.

Perineum.—Two patients had condylomata on the perineum, midway between the anus and the base of the scrotum. Three pedunculated growths, each 1 cm. in diameter, were present in one case, while the other presented two such lesions.

One patient was cured four days after one application of the drug and the other was well in ten days but required two treatments. No pain was experienced in either case. No recurrence has been observed in four months.

Scrotum.—One patient had 25 discrete condylomata, each about 0.5 cm. in diameter, scattered over the left side of the scrotum. Two treatments (with an interval of four days) caused complete disappearance of all lesions in one week without discomfort. There has been no recurrence in three months.

COMMENT.—Tomskey, Vickery and Getzoff have reported excellent results in the treatment of granuloma inguinale with podophyllin. Two such cases which failed to respond to other therapy at this hospital were cured promptly with 25 per cent podophyllin in oil.

The oil suspension and powdered drug have been used by us in removing excessive granulation tissue from surgical wounds with dramatic success. It appears to be far superior to the conventional silver nitrate in this respect.

Podophyllin has been of no value, however, in the treatment of typical, horny verrucae, of condylomata lata of syphilis or of benign rectal polypi.

This drug appears to be most efficacious in removing soft granulomatous tissues, and its clinical applications may not be exhausted. Further studies pertaining to additional therapeutic values of podophyllin are being conducted but as yet are inconclusive.

SUMMARY

Podophyllin has been found to be unusually successful in producing prompt and complete disappearance of condylomata acuminata regardless of size, number, location or duration of the growths. The drug is best applied as a 25 per cent suspension in mineral oil. Anesthesia and hospitalization are not necessary. There is minimal time lost from any type of physical activity.

Most lesions disappear within four days after a single application of the drug. Growths within the urethra usually require two or more treatments. None of our patients required more than four topical applications.

No ulceration or scarring results and the surrounding normal tissue usually is unaffected by the drug. In isolated cases of extensive application under long prepuces some balanoposthitis may develop but thorough washing 24 hours after treatment promises to prevent this and not interfere with the end-result.

The convalescence is usually entirely painless but some patients, especially those with extensive involvement of the vagina, may require sedation.

Recurrences or new growths are to be expected since the etiology of condylomata acuminata remains unknown, but these, likewise, respond quickly and completely to the same treatment.

Podophyllin appears to be capable of destroying most types of granulomatous tissue and additional clinical applicability probably will be forthcoming.

The dramatic results obtained in this series of 200 patients with condylomata acuminata on the penis, female genitalia, perineum, scrotum, urethra and anus, and the simplicity of the treatment with podophyllin, prompt us to recommend more general adoption of this type of therapy.

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